# BEHAVIOURAL AND NEURAL CORRELATES OF AUDITORY EXPECTATION AND THEIR IMPLICATIONS FOR UNDERSTANDING AUDITORY HALLUCINATIONS

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**Thesis submitted for the degree of Doctor of Philosophy of University of Sheffield.**

**Academic Clinical Psychiatry January 2012**

# Abstract

Normal perception relies on predictive coding, in which neural networks establish associations among stimuli and form predictions of expected input. When the actual stimulus does not match the prediction (i.e. it is unexpected) a signal called prediction error is generated. Prediction error modifies expectation and allows correct perception of external sounds. The work presented here investigated the mechanisms of auditory predictive coding in healthy individuals that might relate to abnormal auditory predictions in auditory hallucinations. A task with pairs of associated stimuli was developed in order to induce learning of relationships between visual cues and auditory outcomes. Whilst the majority of the auditory stimuli were presented within the learnt associations (i.e. they were expected), the minority appeared in mismatched pairs (i.e. they were unexpected). It was hypothesised that auditory outcomes that violate the expectation would evoke increased response time and neural activity compared with those that match expectation.

Auditory expectation as induced in the task employed in this work had only a trend-level effect on response time. Functional MRI studies revealed that unexpected, compared with expected, sounds and silences evoked increased activation in the left middle temporal gyrus. Unexpected sounds, but not unexpected silence, versus those expected, evoked greater activation in the left superior temporal gyrus.

The increased response to unexpected, compared with expected, sounds and silences, suggests that left superior and middle temporal gyri are involved in processing auditory stimuli that do not match expectation, i.e. generating auditory prediction error. These findings suggest that the superior and middle temporal gyrus perform different functions in integrating sensory information with predictive signals during auditory perception. The results are discussed in terms of a model of auditory predictive coding in normal perception, and suggest how this model may help explain the occurrence of auditory hallucinations in clinical populations.

# Acknowledgments

I would like to thank Prof. Peter Woodruff and Dr Michael Hunter for supervising this project, Martin Brook for his assistance with the design of the task, Prof. Iain Wilkinson for overseeing the collection of neuroimaging data, Robert Hoskin and Meno Cramer for stimulating discussions, Helen Hickson, Jean Woodhead and Beverly Nesbit for their support. I would also like to thank the radiography staff in the Sheffield Hallam Hospital and all my participants. Finally, my thanks to Bekah Davis and Lotty Greer for being great lab mates on my first year.

I cannot express my gratitude to my family for their love and support. Nie wiem, jak podziękować mojej rodzinie za ich nieustające wparcie. Mama, tata, Teresa, Barbara i Zbyszek – dziękuję za słuchanie, cierpliwe zachęcanie i podtrzymywanie wizji pozytywnego zakończenia. Nick – without your strength, support and encouragement in the darkest hours this PhD project would not be completed. I could not have a better partner.

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# Aims, hypotheses and outline

## General aims

The aim of the work presented in this thesis was to elucidate, employing behavioural and fMRI design, the mechanisms of auditory predictive coding in healthy individuals, to formulate a model of auditory predictive coding in normal perception, and suggest how this model may help explain the occurrence of auditory hallucinations. A task with pairs of associated stimuli was developed in order to induce learning of the relationship between a visual cue (a shape) and an auditory outcome (silence, sound, low-and high-pitched tone, neutral and salient word). Each experiment had two phases: acquisition of associations, followed by mismatch (contrasting expected and unexpected outcomes). Specifically, in the majority of trials the stimuli were presented within the context of the learned pairs (i.e. auditory outcomes were expected), whilst in the minority of trials the stimuli were presented in mismatched pairs (i.e. the auditory outcomes were unexpected).

## Hypotheses

It was hypothesised that response time and accuracy, as well as neural activity in the auditory cortex depend on auditory expectation. Specifically, once participants learned the associations between the visual cue and the auditory outcome, unexpected silence, sound, low-and high-pitched tones would be associated with significantly increased response time and significantly reduced accuracy relative to their expected counterparts. Moreover, unexpected, compared with expected, silence, sound, low- and high-pitched tones and neutral and salient words would evoke significantly increased activity in the auditory cortex. It was also hypothesised that salient words would be associated with significantly greater activity in the auditory cortex than neutral words.

## Outline and specific aims

Chapter 1 – Introduction. This chapter explains the concept of predictive coding and its mechanisms, describes the main existing theories of auditory hallucinations and introduces the expectation-perception model of auditory hallucinations.

Chapter 2 – Method. This chapter briefly explains the theory of associative learning, the principles behind fMRI and connectivity analysis. It also describes general procedure of the fMRI Sound/Silence, Pitch and Salience Experiments.

Chapter 3 -6– Results chapters. These chapters describe the experimental work investigating the mechanisms of auditory predictive coding in healthy individuals, aims, hypotheses, results and discuss the implications of the findings to healthy auditory perception and to auditory hallucinations.

The goal of the behavioural experiments was to investigate the effects of auditory expectation on response time and accuracy as measures of cognitive processing (Chapter 3). Behavioural Sound/Silence Experiment aimed to examine behavioural correlates of processing of expected and unexpected silence and sound, while in Behavioural Pitch Experiment response time and accuracy were investigated in the context of expected and unexpected low-and high-pitched sounds.

The aim of the fMRI experiments was to examine the neural underpinnings of auditory expectation (Chapter 4). In fMRI Sound/Silence Experiment neural activity was examined in response to expected and unexpected silence and sound, while fMRI Pitch Experiment investigated differences in activity in response to expected and unexpected low-and high-pitched sounds.

FMRI Salience Experiment aimed to investigate neural activity underlying the processing of unexpected words of varying salience (Chapter 5). In this study expected neutral words were contrasted with unexpected neutral words and expected salient words were contrasted with unexpected salient words. Data from fMRI Sound/Silence, Pitch and Salience Experiments were analysed together and results described in Chapter 6.

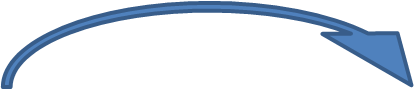
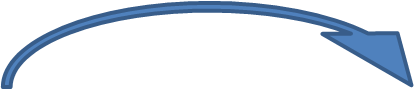
Chapter 7 – General Discussion and Conclusions. This chapter includes discussion of the results of the work presented in this thesis, its conclusions in the context of understanding auditory hallucinations, as well as the limitations and suggestions for future research.

# Chapter 1

# Introduction

## Predictive coding and perceptual expectations

Predictive coding model of perception proposes that normal perception consists of interaction between top-down expectations and bottom-up signals (Figure 1.1). ‘Higher’ cortical areas (i.e. those involved in integrating information) form predictions as to what is likely to occur in the sensory environment. These predictions (or prior expectation) are sent to ‘lower’ areas (i.e. regions involved in early processing of external stimuli) via feedback pathways [(Rao and Ballard, 1999)](#_ENREF_1). Such predictions are based on prior knowledge, learned through a process of establishing patterns between perceived stimuli. Areas that are lower in the cognitive hierarchy aim to reconcile the incoming data with the received prediction. The difference between the prediction and incoming data (prediction error) is sent back to the ‘higher’ cortex via feedward connections. Expected perceptual objects do not have to be processed in as much depth as new or unexpected events. Therefore, predictive representations of incoming stimuli, formed on the basis of the observed associations, allow a reduction in the computational burden (Rao and Ballard, 1999). Whilst stimuli that match the expectation are processed efficiently, it is essential that the perceptual system recognizes events that do not match the prediction because they indicate that learning has failed or that there has been a change in the environment [(Bubic et al., 2010)](#_ENREF_3). The organism (here: human) has to assess the behavioral significance of the stimulus that initiated the signal communicating discrepancy and update its knowledge accordingly [(Friedman et al., 2009)](#_ENREF_4).



**PFC**

**AC**

**Thalamus**

Prediction (*modified*)

Prediction (*modified*)

Input (*prediction error*)

Input (*prediction error*)

**Figure 1.1: Predictive coding in auditory perception.** Each ‘higher’ level sends predictions to the ‘lower’ level, i.e. prefrontal to auditory cortex, and auditory cortex to the thalamus. If the actual input differs from the prediction, the error is signaled by the thalamus to the auditory cortex, and by the auditory to the prefrontal cortex. In healthy perception prediction error serves to modify expectation accordingly. PFC- prefrontal cortex; AC – auditory cortex.

### Neuroanatomy of auditory system

A brief description of the anatomy of auditory system will be helpful in understanding predictive coding and the new model of auditory hallucinations proposed in this thesis. The sound waves first enter the peripheral auditory organs: outer, middle and inner ear [(Boatman, 2006)](#_ENREF_20). The sound wave travels through the outer ear to the tympanic membrane (the eardrum). The tympanic membrane vibrates and sets in motion three bones: mealleus, incus and stapes (the ossicles) in the air-filled middle ear. The motion of the ossicles is processed by the oval window, a membrane which leads to the fluid-filled inner ear. There the sound wave is converted into an electric signal by the hair cells lining the basilar membrane in the cochlea. The hair cells are organized tonotopically, i.e. similar frequencies are processed by topologically neighbouring areas. The electrical potentials travel from the cochlea down the vestibulocochlear nerve to the central auditory system.

The main structures of the central auditory system are the brainstem, the thalamus and the cortex. The auditory information is transmitted to the cochlear nuclei in the brainstem ipsilaterally, i.e. the cochlear nucleus in the left hemisphere receives projections from the left ear and the cochlear nucleus in the right hemisphere receives projections from the right ear. From the cochlear nuclei some projections travel ipislaterally, while others cross the midline and form the lateral lemniscus, which carries the auditory information to the superior olivary complex of the brainstem and then to the inferior colliculus of the midbrain. Hence, the superior olivary complex is the first structure that receives input from both ears and is therefore essential for localization of sound in space (on the basis of binaural cues) [(Tollin, 2003)](#_ENREF_21). The inferior colliculus of the midbrain is the largest of the subcortical auditory structures with abundant connections, e.g. with areas that control motor response to auditory stimuli [(Di Salle et al., 2003)](#_ENREF_22). The functions of this structure include analysis of frequency, detecting source of the sound, filtering of auditory stimuli and processing acoustic cues. From the inferior colliculus the auditory information travels to the medial geniculate nucleus, a thalamic relay station, which in turn projects to the auditory cortex.

The primary auditory cortex is located in the Heschl’s gyrus on the upper bank of the superior temporal gyrus (STG) (Brodmann area 41) [(Bear et al., 2001)](#_ENREF_23). The primary auditory cortex responds to pure tones and processes basic elements of sounds, such as pitch or rhythm, and together with two other areas – rostral field and rostrotemporal field- form the auditory core [(Kaas et al., 1999)](#_ENREF_24). The core projects directly to the surrounding auditory belt. Adjacent to the belt is the parabelt (Brodman area 22), which includes the lateral surface of the posterior STG. The belt and parabelt process more complex sounds. The parabelt has additional functions such as auditory memory. Another important structure on STG is the planum temporale, located anteriorly to the Heschl’s gyrus and involved in functions such as locating sounds in external space [(Hunter et al., 2003)](#_ENREF_25) and distinguishing accents in spoken language [(Adank et al., 2012)](#_ENREF_26). Finally, auditory functions of the middle temporal gyrus (MTG) include processing auditory emotional prosody [(Mitchell et al., 2003)](#_ENREF_27), voice familiarity (in males) (Birkett et al., 2007) and audiovisual integration [(Kilian-Hutten et al., 2011)](#_ENREF_19).

### Neural mechanisms underlying formation of expectation

Regions thought to be involved in generating expectations include prefrontal cortex (PFC) [(Leaver et al., 2009)](#_ENREF_5). This area includes all cortical areas of the frontal lobe, which have a granular layer IV and are located rostrally to the agranular (pre)motor region [(Cerqueira et al., 2008)](#_ENREF_6). The PFC consists of dorsolateral, medial and orbital areas. This region is well placed to formulate predictions, since it integrates information from multiple brain regions [(Miller and Cohen, 2001)](#_ENREF_7). It is also involved in monitoring sensory information and behavioral responses, as well as access of sensory information to awareness [(McIntosh et al., 1998)](#_ENREF_8).

Once generated in the PFC, expectations can be communicated to the auditory cortex. This communication could be served by anatomical connections between PFC and auditory areas [(Miller and Cohen, 2001)](#_ENREF_7). The resulting expectation-driven activity can be initiated in the absence of external input and before the stimulus onset, priming the target cells in the sensory and association cortices [(Engel et al., 2001)](#_ENREF_9). Such priming, which establishes a prior probability of perception, might involve increased firing rate in the target region [(Jaramillo and Zador, 2011)](#_ENREF_10). The state of expectation could be reflected in coordination of neuronal activity, such that populations of neurons in prefrontal and temporal cortices would fire coherently [(Ghuman et al., 2008)](#_ENREF_11). The moments of greatest excitability of these groups of neurons occur in a coordinated, predictable pattern. Thus, the incoming signal consistent with the expectation can be transmitted more effectively than a signal that is transmitted by unsynchronized neurons [(Fries, 2005)](#_ENREF_12). The stimulus would be perceived when the stimulus-evoked signal is summated with the prediction-related activity [(Becker et al., 2011)](#_ENREF_13).

### Neural mechanism underlying prediction error

The prediction error signal is thought to be generated by increased neuronal activity in response to unexpected, compared with expected, stimuli [(den Ouden et al., 2009)](#_ENREF_14). Physiologically, this enhancement in activity following an unexpected outcome might be underpinned by synaptic processes mediated by N-methyl-D-aspartate (NMDA) receptors to glutamate [(Strelnikov, 2007)](#_ENREF_15). If the stimulus does not match the expectation, neurons that are not engaged in synchronized firing have to react to unexpected outcome. These neurons could drive the formation of new neuronal circuits needed to process the surprising stimulus.

In auditory perception, it is thought that prediction error signal is generated in the auditory cortex. Evidence supporting this view involves the phenomenon of mismatch negativity (MMN), an enhanced brain wave potential evoked by a deviant sound in a string of standard sounds [(Naatanen et al., 1982)](#_ENREF_17). Mismatch negativity is assumed to reflect the process of updating auditory predictions [(Winkler, 2007)](#_ENREF_2). It is thought that once generated in auditory cortex, prediction error might be relayed to the frontal areas of the brain, where its behavioral relevance is assessed. The neural representation of such assessment process is assumed to be the increase in activity in ventrolateral PFC, occurring approximately 40 ms after enhanced signal in STG [(Opitz et al., 2002)](#_ENREF_18).

Even if expectation does not match the outcome, the prior probability affects the experience of the incoming stimuli. For example, an indistinct auditory disyllable (between aBa and aDa) following an audio-visual presentation of the lips pronouncing an unambiguous disyllable (aBa or aDa) is likely to be perceived in accordance with that in the video [(Kilian-Hutten et al., 2011)](#_ENREF_19). Such top-down perceptual effect suggests that the brain actively attempts to extract behaviourally relevant signals with maximal efficiency.

## Auditory hallucinations

Hallucinations are involuntary sensory perceptions occuring in the absence of relevant external stimuli in the state of partial or full wakefulness [(Beck and Rector, 2003)](#_ENREF_28). The word ‘hallucination’ is derived from Latin ‘allucinari’, meaning ‘to wander in mind’, ‘dream’ [(Choong et al., 2007)](#_ENREF_29). The first one to use it in its current sense of a perception in the absence of relevant external stimulus is thought to be the psychiatrist Jean-Etienne Esquirol. This definition differentiates hallucination from illusion, which is a misperception of an existing stimulus.

Hallucinations occur in a range of illnesses, e.g. psychotic depression, post-traumatic stress disorder, neurological disorders and deafness [(Beck and Rector, 2003)](#_ENREF_28). Auditory hallucinations are one of the main positive symptoms of schizophrenia, affecting 70% of the sufferers [(Sartorius et al., 1974)](#_ENREF_30). The experience is often so distressing that it contributes to suicidal behaviour [(Nordentoft et al., 2002)](#_ENREF_31). One third to nearly half of the patients with hallucinations will not respond to pharmacological treatment [(Bobes et al., 2003)](#_ENREF_32). Although not as complex and distressing, in some form voices can be experienced by people without mental illness. In some studies 10% of men and 15% of women described hearing voices at some time [(Tien, 1991)](#_ENREF_33). In addition, nearly half of recent widows and widowers hear the voice of their dead spouse [(Carlsson and Nilsson, 2007)](#_ENREF_35). Hallucinations at sleep onset (hypnagogic) and/or upon awakening (hypnopompic) affect 37% and 12.5% of the population, respectively [(Ohayon et al., 1996)](#_ENREF_36).

The universality of hallucinatory experience and similarity in the physical characteristics of the voices indicate that auditory hallucinations are on the continuum of normal perceptual experience [(Beck and Rector, 2003)](#_ENREF_28). The onset of these false perceptions, in both healthy and ill individuals, often follows trauma (not infrequently in childhood) and is in itself very anxiety-provoking [(Romme and Escher, 1989)](#_ENREF_37). The form of hallucinations varies from random mumbled sounds, single words with demeaning content (‘jerk’), frightening commands (‘Die bitch’), running commentary, to conversation involving several voices (Beck and Rector, 2003, Nayani and David, 1996). Their content resembles intrusive thoughts in obsessive-compulsive disorder [(Baker and Morrison, 1998)](#_ENREF_39) as well as fragments of memories or stream of consciousness, often related to past and present preoccupations [(Beck and Rector, 2003)](#_ENREF_28). The voice can be that of a person known to the sufferer, e.g. a neighbour. Often it speaks with an accent different from, although culturally related to that of the patient [(Nayani and David, 1996)](#_ENREF_38). Auditory hallucinations are most often induced by feelings of sadness [(Nayani and David, 1996)](#_ENREF_38) and in periods of stress [(Beck and Rector, 2003)](#_ENREF_28). Those hallucinations that are associated with a mental disorder are typically more frequent, intrusive [(Choong et al., 2007)](#_ENREF_29), negative, unquestioned and unresponsive to corrective feedback [(Beck and Rector, 2003)](#_ENREF_28).

None of the current hypotheses regarding auditory hallucinations fully explains how they arise as perceptions - voices with their own gender, age, accent, emotional tone, loudness and spatial location. Filling this gap in knowledge by clarifying the neural basis of hallucinations could improve the sufferers’ coping, clinical care, and treatment of this often distressing phenomenon. Here we present a view of auditory hallucinations as perceptions and the mechanism of their emergence in both health and illness, based on the accepted principles of modern neuroscience.

## Models of auditory hallucinations

### Reality discrimination

Some contemporary models of this phenomenon seem to agree that those who hear voices mistaken their inner, mental events for external, publicly observable stimuli (Bentall, 1990). Such confusion suggests a deficit in reality discrimination. This misattribution might be due to an impaired ability to recognize one’s own thoughts [(Heilbrun, 1980)](#_ENREF_41). Failure to recognize one’s own communicative intentions (discourse planning), resulting in experiencing own verbal imagery as unintended, and therefore, alien, has also been implicated in auditory hallucinations [(Hoffman, 1986)](#_ENREF_42). The problem of reality discrimination is related to a more common confusion between memories of thoughts and memories of external events (source monitoring) (Johnson et al., 1993). Deficit in this skill might lead to recalling imaginary events as if they actually happened. Strategies employed by healthy people in order to differentiate memories of thoughts from those of real events involve using a range of contextual cues. For instance, an item is more likely to be attributed to an external source if it is recalled more vividly (shares characteristics of real events) or is recalled with less cognitive effort (less intentionally) [(Bentall, 1990)](#_ENREF_40).

According to the reality discrimination model of auditory hallucinations, cognitive impairment in using cues to perform reality discrimination results in perceiving internal events as if they originated from external agents, for instance, a verbal thought misattributed to an external source becomes a false percept [(Bentall, 1990)](#_ENREF_40). These faulty judgements, which do not have to be conscious, arise from an externalizing bias and a tendency to form hasty and inappropriate conclusions in assessing sources of perception. Different types of errors in reality discrimination might give rise to different types of hallucinations. For instance, inability to recognize spatial location might play a role in hallucinations perceived as ‘outside the head’, but not those ‘inside the head’. Deficits in identifying the source of these false perceptions might be maintained by the (subconscious) unwillingness to endorse the self-directed hostility. As reality discrimination is a skill, individual differences might underlie the occurrence of hallucinations in non-clinical population [(Bentall, 1990)](#_ENREF_40).

### Source memory and inhibition

Another factor put forward in explaining hallucinations is an impairment in intentional inhibition, which leads to activation of memories and other current irrelevant mental associations [(Waters et al., 2006)](#_ENREF_45). According to this model, the origins of these auditory percepts are misattributed as a result of inability to bind contextual cues. In support of this view, 90% of patients with auditory hallucinations show the combination of deficits in intentional inhibition and contextual memory. The presence of the problem in a third of non-hallucinating patients suggests that this group is at increased risk of developing auditory hallucinations and that other cognitive processes are important in hearing voices.

### Inner speech/self-monitoring

The inner speech/self-monitoring theory of auditory hallucinations posits that they arise from adefect in the internal monitoring of inner speech (thinking in words) [(Frith, 1987)](#_ENREF_46). According to Frith’s early proposition, symptoms of schizophrenia arise as a result of a failure in the monitoring system, i.e. detection of mismatches between intentions and actions. While the hallucinating individuals fail to recognize their own intention to think (willed action), they perceive the ‘corollary discharge’ – a copy of the information about the intended action sent to the sensory areas. This ‘dissociation between will and action’ leads to a misattribution of the percept to an external source. Indeed, when imaging speech, individuals with auditory hallucinations fail to activate areas involved in the normal monitoring of inner speech (rostral supplementary motor area and left middle temporal gyrus) [(McGuire et al., 1996)](#_ENREF_47). Therefore, the inability to recognize the inner speech as self-generated might be due to the abnormal connectivity between areas that produce the speech and those that monitor it (‘mind’s voice and mind’s ear’) [(McGuire et al., 1996)](#_ENREF_47).

Recently, this theory has been placed in the context of predictive coding and the emphasis shifted from the failure in detecting intention to failure of the corollary discharge [(Stephan et al., 2009)](#_ENREF_48). It is proposed that hallucinations arise when failure to encode uncertainty in reconciling the top-down and bottom-up signalling gives too much influence to the prior expectation in explaining the external stimulus, leading to a false inference (Friston, 2005). According to this stance, prior expectation cannot be generated in the absence of incoming stimuli. Hence, neither a prediction on its own nor the bottom up information will produce hallucination; false perception results from the interaction of the two. Since uncertainty is encoded by cholinergic neurons, it is the dysfunction of this system that is proposed to underlie the imbalance between prior expectations and bottom-up stimuli.

The corollary discharge is a ‘special case’ of predictive coding [(Stephan et al., 2009)](#_ENREF_48). Normally, it allows to predict the sensory consequences of one’s actions, and, consequently, subtract the prediction from the actual incoming data. If the prediction matches the external sensory input then the sensation is assumed to be self-generated and is cancelled. To illustrate, a corollary discharge sent from the frontal areas (which produce thoughts) would forewarn the temporal areas that the forthcoming inner speech is self-generated. Abnormal connectivity, however, gives rise to a dissociation between the motor act (in this case, thinking) and its sensory consequences, and a misattribution of the latter to an external source. Since corollary discharge involves synaptic plasticity, in particular short term potentiation regulated by dopamine and serotonin, abnormality in regulating synaptic plasticity in schizophrenia would contribute to the misattribution of inner speech [(Stephan et al., 2009)](#_ENREF_50).

### Auditory-perceptual model

In order to explain the acoustic characteristics of auditory hallucinations, they might need to be approached as perceptions, generated by dysfunctional primary and secondary auditory cortex [(Hunter, 2004, Woodruff, 2004, Hunter and Woodruff, 2004)](#_ENREF_51). Involvement of the auditory cortex in generating hallucinations is implied by the findings that areas of the brain involved in normal speech perception are abnormally activated during hallucinations [(McGuire et al., 1993, Woodruff et al., 1995, Shergill et al., 2000)](#_ENREF_54). In addition, it has been reported that the volume of STG is inversely correlated with the severity of the voices [(Barta et al., 1990)](#_ENREF_57). Auditory hallucinations are associated with reduced response of the right MTG to external speech, which suggests that the same cortical resources are involved in recognizing both false and real perceptions (saturation hypothesis) [(Woodruff et al., 1997)](#_ENREF_58).

#### 1.3.4.1. Externality of auditory hallucinations

In healthy males, hearing voices in external auditory space is accompanied by activation in the left planum temporale (Hunter et al., 2003). This suggests involvement of this area in processing the spectro-temporal features of the voices, which enables their localization in the external space. Perception of the hallucinated voices as external might therefore be associated with abnormal activation of planum temporale. Evidence of malfunction of this structure comes from the finding that, compared to healthy controls [(Guterman and Klein, 1991)](#_ENREF_59) and to non-hallucinating patients [(Heilbrun et al., 1983)](#_ENREF_60), individuals with external auditory hallucinations (perceived as originating ‘outside the head’) have difficulties with spatial localisation of real sounds. In addition, the progressive change of auditory hallucinations in schizophrenia from external (perceived as originating ‘outside’ the head) to internal (perceived as originating ‘inside the head’) (Nayani and David, 1996) might be associated with the observed reduction of the volume of planum temporale [(Kasai et al., 2003)](#_ENREF_61).

#### 1.3.4.2. Gender of the ‘voices’

Reduced ability of auditory processing might underlie the predominance of male voices in hallucinations. During auditory gender attribution female voices induce greater response in the right anterior STG than male voices (Sokhi et al., 2005, Lattner et al., 2005). This suggests that female voices are more acoustically complex and thus more difficult to generate than male voices [(Sokhi et al., 2005)](#_ENREF_62). Thus, male voices are easier to produce and more frequent.

#### 1.3.4.3. Prosody and familiarity of auditory hallucinations

Another important feature of speech, prosody, is processed by the temporal lobe in the right hemisphere (Mitchell et al., 2003, Wiethoff et al., 2008,). Abnormal activity in the right MTG in male hallucinating patients [(Shergill et al., 2000, Woodruff et al., 1997)](#_ENREF_66) suggests that hearing voices might be underlied by a dysfunction of this area. Familiar ‘voices’, common in auditory hallucinations (Nayani and David, 1996), could be generated by the lower bank of the superior temporal sulcus, an area shown to activate in response to voice familiarity in males [(Birkett et al., 2007)](#_ENREF_67).

#### 1.3.4.4. Laterality of auditory hallucinations

A general dysfunction of the left hemisphere, expressed by a lack of functional asymmetry, might also contribute to auditory hallucinations [(Hunter, 2004)](#_ENREF_51). In healthy individuals auditory processing is characterized by the ‘right ear advantage’, i.e. greater accuracy in identifying spatial location of speech signals coming from the right versus left hand side [(Kimura, 1961)](#_ENREF_68). In schizophrenia this asymmetry is reduced, i.e. response to external speech is reduced in left STG but can be increased in the right MTG, compared with healthy volunteers (Woodruff et al., 1997, van Veelen et al., 2011). External hallucinated voices usually come from the right side of space [(Nayani and David, 1996)](#_ENREF_38). Hence, the dysfunction of the left hemisphere or the altered balance between the left and right hemisphere might play a role in the genesis of auditory hallucinations.

#### 1.3.4.5. Saturation hypothesis

The finding that external speech evokes reduced response in the right MTG during severe hallucinations, compared with activity in the same patients after treatment, led to the saturation hypothesis [(Woodruff et al., 1997)](#_ENREF_58). According to this proposition, auditory hallucinations engage the hearing apparatus (STG and MTG) such that they compete with external speech for shared neurophysiological resources within the temporal cortex. Similarly decreased activation, relative to those who do not hallucinate, is evoked by tones in left primary auditory cortex of those who hear voices [(Ford et al., 2009)](#_ENREF_70). Authors of this study conclude that reduced response to external stimuli also suggests that hallucinations are the anticipated sensory experience. The primary auditory cortex might be ‘turned on’ and ‘tuned in’ to internal processes rather than external percepts.

#### 1.3.4.6. Endogenous neural activity

The auditory-perceptual model relies upon the existence of a neural substrate for auditory hallucinations in a healthy brain [(Hunter et al., 2006)](#_ENREF_71). During silence endogenous neural activity in the primary and association auditory cortex may be modulated by anterior cingulate cortex (ACC). Dysfunction of this temporo-cingulate network might lead to generation of false percepts, e.g. as transient representations of phonetic patterns stored in memory. A misinterpretation of the physiological activity could take place in the state of disease [(Hunter, 2004)](#_ENREF_51). Evidence suggests that the risk for developing psychotic symptoms such as auditory hallucinations lies on the continuum that overlaps with healthy population [(Sommer et al., 2008)](#_ENREF_34). Hence, dysfunctional activity in auditory cortex that underlies false percepts might occur both in patients, and those not diagnosed with mental illness.

## The gap in the existing explanations for auditory

## hallucinations

None of the existing models of auditory hallucinations, including the reality discrimination, the source memory inhibition, the inner speech/self-monitoring or the auditory-perceptual theories, fully explain the mechanisms or phenomenological features of the ‘voices’. The reality discrimination model is helpful in explaining the types of auditory hallucinations and their presence in both mentally ill and healthy individuals. However, evidence in support of this model is inconsistent [(Aleman et al., 2003)](#_ENREF_72). In addition, reality discrimination deficit has been found in other groups (Foley and Ratner, 1998, Henkel et al., 1998), who do not suffer from hallucinations, suggesting there might be no straightforward relationship between the reality discrimination deficits and hearing ‘voices’. The source memory and inhibition model helps to explain both the content and the unwanted nature of auditory hallucinations. The inner speech/self-monitoring model of auditory hallucinosis bridged the gap between the cognitive and physiological level of explanation. Thinking as the special case of action can aid in explaining the content of hallucinations. Framing hallucinations in the predictive coding model is particularly helpful in the light of the current view of cognition, which emphasises the importance of prediction in everyday perception (Summerfield and Egner, 2009, Bubic et al., 2010).

However, none of the current models of auditory hallucinations explain how thoughts acquire the perceptual and acoustic qualities that characterise both real speech and hallucinated voices. The inner speech/self-monitoring hypothesis could be better suited to explain a phenomenon where own speech is perceived as ‘alien’, or the phenomenon of thought insertion, where the person attributes their thoughts to an external agency [(Pierre, 2009)](#_ENREF_76). Some phenomenological aspects of auditory hallucinations indicate that misattribution, the focus of the inner speech hypothesis, might be a consequence, rather than a cause, of auditory hallucinations [(Hoffman et al., 2000)](#_ENREF_77). Neither does the inner speech/self-monitoring model explain why not all the internal discourse becomes hallucinations, as shown by the finding that the majority of those who hallucinate can differentiate between their normal verbal thoughts and the ‘voices’ [(Hoffman et al., 2008)](#_ENREF_78). Another aspect that is not well accounted for in the framework of inner speech/self-monitoring is the occurrence of auditory hallucinations in individuals not diagnosed with mental illness.

The auditory perceptual hypothesis focuses on the final stage of generation of perceptions in the absence of auditory input, from abnormal activity in the areas which subserve attributes of auditory input such as gender, prosody, familiarity and externality. According to this view, acoustic characteristics of auditory hallucinations are determined by the same auditory cortical mechanisms that determine characteristics of external auditory objects. It is not clear, however, how activation of the parts of auditory system which subserve the acoustic and perceptual characteristics of auditory hallucinations, leads to the generation of perceptions with meaningful content and individual relevance. Neither does the auditory perceptual hypothesis explain why the auditory cortex would be activated abnormally and generate these false percepts, either in health or illness. In short, while the inner speech/self-monitoring hypothesis attempts to explain the cause and content, but not the perceptual features of the voices, the auditory perceptual hypothesis elucidates the generation of the acoustic characteristics, but not the content or the underlying mechanism of hallucinations.

The new hypothesis presented in this thesis attempts to fill the gap in the existing explanations. It incorporates the concept that the brain has a generic ability and substrata to produce false percepts [(Hunter et al., 2003)](#_ENREF_25). We propose that auditory hallucinations are perceptions driven by mental states [(Behrendt, 1998)](#_ENREF_79) and formed in the process of predictive coding. However, perceptual predictions, which give rise to hallucinations, can be generated in the absence of external sensory input. The inner speech/self-monitoring model suggests that hallucinations arise when the internally generated verbal sensation is unexpected and thus misattributed [(Stephan et al., 2009)](#_ENREF_48). We propose the converse: expectations are translated into false perceptions because auditory cortex anticipates them. In our view, auditory hallucinations are sometimes interpreted by the sufferer as generated by an external agency not because they are misattributed in the first place, but because they have the acoustic qualities of real percepts. This new hypothesis has an additional capacity to explain the genesis of auditory hallucinations in the diversity of conditions, including the continuum of the risk for mental illness in the general population.

## Expectation –perception model of auditory hallucinations

### Hypothesis

It is thought that in normal perception predictive representations of forthcoming sensory input are formed in the prefrontal areas and communicated to sensory cortex [(Rahnev et al., 2011)](#_ENREF_80). Our hypothesis is that, in auditory hallucinations, the predictions of input are relatively unconstrained by prediction error and erroneously identified as representations of actual auditory signal evoked by external stimulation. We suggest that this is the key process leading to the experience of hallucinations.

### Expectation-perception model: mechanisms

In the majority of people expectations do not lead to hallucinations because the prior probability is modulated by the stimulus-driven activity. The ascending neural pathways deliver to the auditory cortex the sensory input that does not match the prediction and the prior expectation is corrected. Failure of this ‘correction’ mechanism may occur when transmission of auditory information consistent with the expectation is enhanced, when the transfer of information that does not match the prediction is suppressed and when the prediction is so broad that random fluctuations of activity in auditory cortex lead to generation of an auditory percept in the absence of external stimuli (see Figure 1.2). These mechanisms might lead to either impaired transmission of prediction error or to its absence. The lack of modulation of expectation by bottom-up signals may occur on the continuum of the schizotypal tendencies in the population.

#### Abnormal modulation of thalamus by prefrontal cortex

The prefrontal cortex could enhance the transmission of information supporting the prior probability and inhibit the transmission of information that does not match expectation from the thalamus to the auditory cortex (see Figure 1.3). Such a situation might prevent the auditory cortex from generating a prediction error signal and lead to a state where prediction is interpreted as an actual auditory input (auditory hallucination). Indeed, PFC in primates has particularly widespread projections to the thalamic reticular nucleus (TRN) [(Zikopoulos and Barbas, 2006)](#_ENREF_81). Exceptionally large axonal boutons on these projections could allow PFC to enhance transmission of input consistent with expectation and inhibit communication of input that does not match the expectation. Through such modulation PFC might control the flow of information from the thalamus to the cortical structures, e.g. temporal association cortices.

The ability of the PFC to modulate the input at the level of the thalamus is likely to increase the efficiency of perceptual processing in healthy individuals. For example, a lesion of rat TRN renders the animal unable to benefit from a spatial cue in an attention orienting task [(Weese et al., 1999)](#_ENREF_82). The detrimental effect of thalamic lesion on the rat’s performance supports the view that through its modulation of TRN, the PFC allows the organism to ignore multiple irrelevant stimuli in the environment and focus its response on the most significant events [(Barbas and Zikopoulos, 2007)](#_ENREF_83).

Healthy modulation of sensory input by the PFC facilitates perception, while still allowing for correction of the prediction and adaptation of response. Evidence suggests that in schizophrenia, however, there are fewer than normal ascending projections from the mediodorsal thalamic nucleus to PFC [(Lewis and Sweet, 2009)](#_ENREF_84). Hence, there might be an imbalance in the flow of information between the PFC and the thalamus, in favor of the descending, expectation-driven transmission. In addition, the nature of the PFC influence on the thalamus might depend on the state of balance between the frontal parts of the brain. The posterior orbitofrontal cortex (OFC) is important in processing emotional information [(Woodruff, 2004)](#_ENREF_52), has more incoming than outgoing connections with amygdala [(Ghashghaei et al., 2007)](#_ENREF_85) and is dedicated to evaluating the emotional significance of stimuli [(Rolls and Grabenhorst, 2008)](#_ENREF_86). In a state of anxiety activation of amygdala could, through its ascending projections, increase activity in the posterior OFC [(Barbas and Zikopoulos, 2007)](#_ENREF_83). Through the extensive connections between the OFC with TRN, the amygdala-led modulation could then attenuate thalamic processing of stimuli inconsistent with expectation.

**Figure 1.2. The mechanisms underlying auditory hallucinations in the expectation-perception model.** The PFC primes auditory cortex for expected input. Transmission of the expectation from the PFC to the thalamus might result in the selective bottom-up transfer of information. Under these circumstances the signals that match expectation are enhanced, whereas those that do not match the expectation are attenuated. As a result, the auditory cortex receives mainly auditory input that is consistent with the expectation. Anatomical abnormalities in neurons, neurotransmitter imbalance and dysfunction of auditory cortex result in deficient processing of prediction error. The prior probability is so broad that random fluctuations in spontaneous activity might enhance the endogenous signal so that it becomes a conscious percept in a recursive exchange between the PFC and the auditory cortex. PFC – prefrontal cortex.

PFC

Broad prior probability

Thalamus

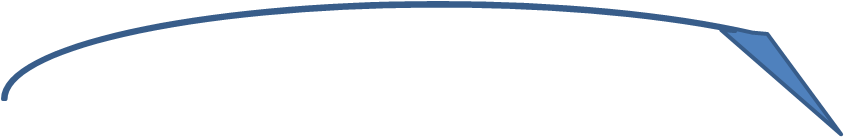
Auditory cortex

(exaggerated spontaneous activity)

Abnormal modulation

Selective/impaired transfer of input

Neurotransmitter dysfunction



Animal models provide evidence that psychosis is partly underpinned by increased spontaneous activity of pyramidal cells in OFC [(Homayoun and Moghaddam, 2008)](#_ENREF_87). Moreover, this area has been found to be hyperactive in actively hallucinating individuals [(Silbersweig et al., 1995)](#_ENREF_88), as well as during listening to the previously hallucinated words [(Bentaleb et al., 2006)](#_ENREF_89). Such increased activity of OFC could enhance the influence of the amygdala on the thalamus such that processing of the stimuli inconsistent with the expectation could be reduced and transmission of the signal confirming the prediction enhanced.

If bottom-up transmission of information that supports the expectation generated by the PFC is enhanced at the cost of prediction error, frontal areas might interpret this communication as a signal corresponding to an external stimulus that matches the prediction. The same prior probability might then be sent again, amplified, by the top-down pathways to the auditory cortex. Thus, a feedback loop would be created, which allows the prior probability to grow by attracting more probability. Hence, reduced feedforward pathways from the thalamus to the PFC in combination with the hyperactivity of OFC might increase the strength of the top-down expectations and their influence on early auditory processing to such extent that prediction error is either severely attenuated or not transmitted.

#### Absence or impaired transmission of external input

The influence of expectation increases when external input is reduced and prediction error, even if generated, is too weak to balance the top-down process. Healthy individuals can experience auditory hallucinations of voices and music in conditions of silence combined with selective auditory attention [(Knobel and Sanchez, 2009)](#_ENREF_90). Hallucinations in these circumstances might be underpinned by increased activity in both PFC and auditory cortex, induced by attention [(Voisin et al., 2006)](#_ENREF_91). Impaired processing of auditory information might also contribute to the imbalance between the expectation and the signals corresponding to actual incoming stimuli. This might be the case in musical hallucinosis experienced by individuals with acquired deafness [(Griffiths, 2000)](#_ENREF_92). Attenuated processing of external input in combination with greater than normal auditory sensitivity might underlie the hypnagogic and hypnopompic hallucinations in healthy individuals. It has been found that those who experience sleep-related auditory hallucinations show increased auditory sensitivity and increased activity of the regions putatively modulating auditory cortex in a condition of increased attention, relative to those who do not hallucinate [(Lewis-Hanna et al., 2011)](#_ENREF_93). It is plausible that auditory cortex of these individuals is still relatively hyperactive even when sleep is initiated and the brain reduces conscious processing of external input. In such circumstances, more temporal cortex neurons could be available to synchronize with PFC neurons. As processing of sounds is altered in preparation for sleep, processing of prediction error would be reduced. As a result, the prior probability would be more likely to become a percept.

In schizophrenia neurons in the feedforward pathways within the auditory cortex are impaired, as evidenced by reduced density of axon terminals [(Sweet et al., 2007)](#_ENREF_94) and smaller somal volumes of pyramidal cells [(Sweet et al., 2004)](#_ENREF_95). The deficit in the ascending pathway might lead to an impairment in communicating the external input (or lack of it) to the auditory cortex. Whilst such anatomical abnormalities in the feedforward pathways are not sufficient to result in a hearing impairment, they might lead to inadequate representation of auditory input in auditory cortex. An outcome of impaired communication could be a failure in generating prediction error or generation of an attenuated prediction error. As a consequence, the prior expectation would dominate the perception and hallucination might arise.

#### Impaired neurotransmitter function and abnormal connectivity

The processing of the prediction error signal requires changes in connectivity between brain regions [(den Ouden et al., 2009)](#_ENREF_14), as well as formation of new neuronal pathways, mediated by NMDA receptors [(Strelnikov, 2007)](#_ENREF_15). Functional connectivity within the brain relies on plasticity between areas, regulated by monoaminergic and cholinergic neurotransmitters (dopamine, norepinephrine, serotonin, acetylcholine), as well as NMDA-receptors for glutamate [(Friston, 1998)](#_ENREF_96).

**PFC** (including OFC)

**Thalamus**

**AC**

**Figure 1.3. The hypothesized thalamus modulation by PFC in auditory hallucinations.** The PFC might transmit the prior probability via its abundant projections to the thalamus (black arrow), thus enhancing the transmission of information consistent with expectation (dashed black arrow) and attenuate transmission of ‘irrelevant’ signals (grey arrow) from the thalamus to the auditory cortex. Such filtering of information might be increased when ascending projections are reduced or when hyperactivity in the OFC further enhances its influence on the thalamus. Under these circumstances the auditory cortex might fail to generate a prediction error signal and prediction could be interpreted as an actual auditory input. PFC – prefrontal cortex, OFC- orbitofrontal cortex, AC – auditory cortex.

Abnormal connectivity has been found in stress-related conditions in individuals not diagnosed with schizophrenia. For instance, post-traumatic stress disorder is associated with abnormal, both increased and decreased, connectivity of the thalamus with other brain areas [(Yin et al., 2011)](#_ENREF_97). Compared with controls, healthy women who undergo Mindfulness-Based Stress Reduction therapy show enhanced connectivity within auditory and visual networks, as well as between auditory areas and regions involved in attention and self-referential processing [(Kilpatrick et al., 2011)](#_ENREF_98). Such alteration in functional connectivity as a result of reduced stress suggests that anxiety might be associated with decreased interactions between auditory cortex and other brain areas. Reduced connectivity of auditory cortex could, in turn, impair the processing of prediction error.

Stress-related changes in connectivity and resulting reduction in prediction error might be underpinned by modifications in neurotransmitter levels. For instance, it has been found that stress leads to increased noradrenergic activity of the central nervous system [(Geracioti et al., 2001)](#_ENREF_99). In addition, cognitive-behavioral stress management interventions reduce anxiety and urinary output of noradrenaline, suggesting decreased levels of noradrenaline with decreased stress [(Antoni et al., 2000)](#_ENREF_100). Stress enhances dopamine release in the nucleus accumbens and in the PFC and leads to an increase in acetylcholine release in the hippocampus [(Imperato et al., 1992)](#_ENREF_101). Hence, stress-related changes in levels of neurotransmitters might affect connectivity and impair processing of prediction error signal in healthy individuals subject to stress, leading to the formation of auditory hallucinations.

According to the disconnection hypothesis of schizophrenia, the symptoms of this illness arise as a result of abnormal plasticity involving both insufficient and exuberant functional connections between brain areas [(Friston, 1998)](#_ENREF_96). Postmortem and genetic studies found evidence of a hypofunction of NMDA receptors in schizophrenia [(Coyle, 2006)](#_ENREF_102). NMDA receptors, themselves regulated by dopamine, serotonin and acetylcholine, modulate synaptic plasticity [(Stephan et al., 2009)](#_ENREF_48). Schizophrenia is also characterized by decreased dopamine activity in prefrontal areas, and increased dopamine function in striatal regions [(Davis et al., 1991)](#_ENREF_103). Functional connectivity in schizophrenia can be both reduced, e.g. between the middle temporal and postcentral gyrus, and increased, e.g. between the thalamus and the cingulate cortex [(Skudlarski et al., 2010)](#_ENREF_104). Generation and communication of prediction error requires connectivity between different brain areas, e.g. those processing the cue and those processing the outcome (den Ouden et al., 2009). Thus, neurotransmitter abnormalities and underlying aberrant connectivity, combined, could impair processing of prediction error, leading to an enhanced role of prediction in shaping the final percept, and potentially to auditory hallucinations.

##### Spontaneous exaggerated activity and a broad prior probability

In those prone to auditory hallucinations, spontaneous fluctuations of neuronal activity observed in the speech-sensitive regions in healthy auditory cortex during silence [(Hunter et al., 2006)](#_ENREF_71) can be exaggerated. Such hyperactivity is suggested by evidence of increased auditory sensitivity and activity in areas putatively modulating auditory cortex [(Lewis-Hanna et al., 2011)](#_ENREF_93). Spontaneous exaggerated fluctuations in neuronal activity can be incorporated into the prior probability set up in auditory cortex by frontal areas. Such incorporation could amplify the signal sufficiently for it to become a percept (i.e. an auditory hallucination). Here, the additive effect of the prediction-related and the spontaneous activity would mimic physiological generation of a percept from activity related to prior probability combined with stimulus-evoked activity [(Arieli et al., 1996)](#_ENREF_105).

We propose that, in addition to being generated by excessive activity, representations of the ‘voices’ in the auditory cortex (i.e. the number of neurons that respond selectively to those false percepts) are abnormally large. Normal enhancement of neural representations has been noted for frequently perceived stimuli, e.g. piano tones in skilled musicians [(Pantev et al., 1998)](#_ENREF_106). A reflection of abnormally large representations of hallucinatory percepts might be the increased neural activity shown by those suffering from hallucinations in response to emotional words specific to the content of their voices [(Sanjuan et al., 2007)](#_ENREF_107). Therefore, the hallucinatory stimuli might be represented by abnormally high numbers of neurons that act as a substrate for relatively broad prior probability.

In some circumstances the broad prior probability in auditory cortex might encounter a cluster of neurons that is currently engaged in responding to an external stimulus. If the output of the stimulus-processing neurons is incorporated into the anticipatory activity, the characteristics of the signal arising from sensory stimulation might become part of the false percept. This could be the case in hallucinations referred to by Dodgson and Gordon [(2009)](#_ENREF_108) as ‘hypervigilant’, where fragments of speech or sounds like a cough are interpreted within the template of the prior expectation. Functional hallucinations might be another example of an incorporation of external stimuli into a perceptual prediction. In these circumstances the timbre, prosody and pitch of the false perception match those of the real sounds (e.g. voices that occur concurrently with sound of water) (Hunter and Woodruff, 2004, Warren and Griffiths, 2003).

### Recursive exchange

We propose that prior probability, abnormally large and combined with exaggerated fluctuations in neuronal activity, develops into a false percept in a recursive exchange. In our view, the initial prediction which gives rise to a hallucinatory auditory percept is not a conscious verbal representation. Rather, it might arise as a nonverbal, not fully formed representation, outside of awareness and consisting of certain basic features of the predicted stimuli. The process of shaping and specification of this initial vague representation is similar to that which underlies normal perception. Studies of visual processes suggest that attributes of a given object are elucidated gradually, starting with the holistic formulation of the object and progressing through a more detailed analysis of the structure of the percept [(Luu et al., 2010)](#_ENREF_110). For example, a brief presentation of fragmented and scrambled images is associated with activity in the medial OFC, followed by response in the regions involved in object recognition. Activity in the medial OFC is thought to underlie the processing of the initial ‘gist’ of meaning, i.e. the intuitive judgment, which integrates the briefly presented, ambiguous information. This initial ‘guess’ is then sent back to the ‘lower’ areas involved in perception, where it influences the formation of the full, explicitly understandable representation of the viewed object. Such initial intuitive judgment might be based on the subconscious activation of the semantic object representations [(Bolte and Goschke, 2008)](#_ENREF_111).

This ‘top-down’ facilitation reduces the time and computational effort through eliminating many of the possible interpretations of the given input. The progressive nature of the perceptual process is reflected in the functional hierarchy, in which ‘higher’ cortical areas analyze abstract properties of the stimuli, whereas early sensory regions respond to and construct objects from physical attributes [(Nelken, 2008)](#_ENREF_112). For instance, the process of understanding speech involves areas responding to abstract, non-acoustic features of speech (inferior frontal gyrus, temporal cortex surrounding auditory cortex), those responding to concrete, acoustic properties of speech (auditory belt and parabelt) and regions sensitive to sub-speech properties of sounds (primary auditory cortex) [(Davis and Johnsrude, 2007)](#_ENREF_113).

Prefrontal cortex might generate a subconscious, not fully formed prediction of an auditory object in the absence of or before the onset of the stimulus. Such prediction would consist of the main prototypical features, e.g. a feeling of impending threat. This representation would then be sent directly to the auditory cortex and the thalamus, biasing their activity. Auditory cortex would also send the prior probability to the thalamus independently of the PFC. The thalamus, abnormally modulated by the PFC, and having received ‘double’ prior probability, could then transmit information largely matching the expectation to the auditory and prefrontal cortices. Any signal discordant with the prediction would not be communicated due to insufficient plasticity, neuronal abnormalities in the feedforward pathways and dysfunction of the auditory cortex. Thus, the PFC would receive a bottom-up signal still relatively vague, but in accordance with the initial prior probability. A stronger and more specific, confirmed expectation could then be sent again to ‘lower’ areas. Spontaneous synaptic currents might fluctuate randomly within the area of the broad anticipatory activity in the auditory cortex. Hence, the shape of the forming percept might be biased towards the attributes served by the area of the fluctuation. For example, association areas of auditory cortex might imbue the signal with acoustic and meaningful properties such as male gender (easier to procure than female timbre), familiar voice (processed by the MTG) and particular words. Thus the vague prediction would be rendered more concrete. Such incorporation of random firing might move the activity pattern to a higher level, which would result in approximation of an additive effect of a stimulus-related signal with anticipatory activity. The signal returning to the PFC could be interpreted as one matching the prediction and thus, reinforce the expectation. A final percept, e.g. a sentence spoken by a familiar male voice enticing to self-harm, could result from this recursive exchange.

### Predictions and implications of the expectation-perception hypothesis

The most important prediction of the expectation-perception hypothesis is that individuals suffering from auditory hallucinations should show attenuated prediction error processing. Reduced mismatch negativity (MMN), thought to reflect updating of predictions [(Winkler, 2007)](#_ENREF_2), has been observed in patients who suffer from hallucinations compared with healthy controls and patients who do not hallucinate [(Fisher et al., 2008)](#_ENREF_114). Specifically, those with schizophrenia show reduced MMN in response to frequency, but not duration or intensity deviants. Reduction in MMN in people prone to hallucinations is manifest in response to all three types of deviants. Attenuation of MMN in response to duration and intensity deviants is correlated with severity of auditory hallucinations in patients with schizophrenia [(Fisher et al., 2011)](#_ENREF_115). In addition, among patients with schizophrenia experiencing auditory hallucinations, greater severity of the ‘voices’ is associated with greater reduction in the amplitude of MMN in the left hemisphere [(Youn et al., 2003)](#_ENREF_116). Although auditory processing has not been studied in the ketamine model of psychosis, NMDA antagonist ketamine disrupts processing of prediction error in cognitive tasks performed by healthy volunteers [(Corlett et al., 2006)](#_ENREF_117). Here, the disruption was reflected in the lack of normal increase in activity of right PFC. Enhanced signal in the right PFC indexes processing of unpredicted cognitive information. Psychotic patients, including those with hallucinations, show similarly disrupted cognitive processing of prediction error as healthy volunteers administered ketamine [(Corlett et al., 2007)](#_ENREF_118). Optimally, the hypothesis of reduced auditory prediction error could be investigated with auditory tasks, where cues would be associated with and predict auditory stimuli.

The emphasis on the imbalance between the prior expectations and the external input in the genesis of auditory hallucinations leads to a prediction that the top-down processing might have greater effect on perception in voice hearers than in non-people prone to hallucinate. Indeed, imagery has greater influence on perception in the auditory modality in patients with more severe hallucinations. Specifically, a previously imaged stimulus is detected significantly better than a stimulus that was not imaged [(Aleman et al., 2003)](#_ENREF_72). Compared with those free of hallucinations, non-clinical groups of people prone to hallucinate show significantly greater tendency to report hearing a non-existing voice in white noise [(Barkus et al., 2007)](#_ENREF_119). They also have a propensity to identify a masked word as the word congruent with the sentence context [(Vercammen and Aleman, 2008)](#_ENREF_120). These findings suggest an increased effect of top-down processes on perception in those prone to hallucinating on the semantic processing level.

Results of the studies showing increased neural activity in response to emotional, previously hallucinated words in those who suffer or used to suffer from hallucinations [(Sanjuan et al., 2007)](#_ENREF_107) could be interpreted as reflecting an increased size of representations of stimuli that are often present in auditory hallucinations. Such abnormally large representations could translate into aberrantly broad prior probability. This prediction could be tested in more detail in studies focusing on perceptual expectations in voice hearers.

The expectation-perception hypothesis of auditory hallucinations has important implications for their understanding and treatment. It might be possible to reduce the absolute and relative overactivity of the OFC with transcranial magnetic stimulation or transcranial direct current stimulation. The same methods could be used to stabilize activity in auditory cortex (Giesel et al.,2011, Homan et al.,2011). Since anxiety affects connectivity, stress-reducing therapies might be beneficial in improving functional integration between brain areas [(Kilpatrick et al., 2011)](#_ENREF_98). Potentially useful pharmacological treatments could include drugs regulating neurotransmitter function, as well as kinases, which affect the size, number and function of dendritic spines, and thus both structural and functional plasticity (e.g. kalirin-7) [(Penzes and Jones, 2008)](#_ENREF_123). Coping strategies based on distraction (e.g. listening to music) might relieve the severity of auditory hallucinations by drawing attention away from the internal percepts and towards external stimuli, thus enhancing processing of bottom-up information by feedforward pathways.

### Summary

In this chapter we aimed to present a hypothesis of auditory hallucinations that would explain the mechanism of the ‘voices’ and fill the gaps left by the existing explanations. We propose that auditory hallucinations arise from abnormalities in predictive coding which underlies normal perception. Such abnormalities can occur on the continuum of risk for developing psychotic symptoms in the population. The suggested dysfunction includes absence or attenuation of prediction error and resulting dominant role of expectation in the formation of the final percept. The deficiency in the processing of prediction error might arise from abnormal modulation of the thalamus by the PFC, the absence or impaired transmission of external input, a dysfunction of auditory cortex and neurotransmitter systems, as well as from abnormal connectivity. At the same time, the prior probability is aberrantly broad and so likely to be amplified by the exaggerated fluctuations in the spontaneous activity in the auditory cortex. Since there is no prediction error, the initially vague prior probability develops into a concrete, explicit percept even in the absence of external input, as a result of a recursive pathological exchange between ‘higher’ and ‘lower’ brain areas.

## Conclusions

The expectation-perception model agrees with the general assumption of Friston’s [(2005)](#_ENREF_49) proposition concerning the role of the imbalance between the prediction and the actual sensory input. However, in our view the ability of predictions to arise in the absence of any external input is crucial in the generation of auditory hallucinations, since often they occur in silence or when individual is alone. We also propose concrete mechanisms leading to the imbalance between the expectation and the external input. Whilst both inner speech/self-monitoring and expectation perception hypotheses appreciate the importance of prediction error in the occurrence of auditory hallucinations, they diverge on the point concerning its role. According to the updated inner speech/self-monitoring hypothesis, false percepts arise when the auditory cortex fails to receive the prediction of inner speech, i.e. the efferent copy of the initiation of thinking in words [(Stephan et al., 2009)](#_ENREF_48). Under these circumstances, hallucinations seem to be the result of the large prediction error (sensation of speech in the absence of forewarning prediction). We have not, however, found evidence in existing research of increased prediction error in individuals suffering from hallucinations. On the contrary, the phenomenon considered to reflect the process of updating auditory prediction, mismatch negativity, is reduced in schizophrenia and in particular in voice hearers. Therefore, we propose an alternative view, in which auditory cortex is primed to perceive the predicted input, and it is the absence of prediction error that gives rise to the false percepts. We also propose that rather than arising as inner speech, voices are generated in a recursive exchange between the prefrontal and the auditory cortex, largely outside of the individual’s awareness. The expectation-perception model of auditory hallucinations offers a comprehensive explanation of the mechanism of auditory hallucinations in both health and disease, and has the potential to contribute to development of more effective treatments.

## Overview of the experimental work

In order to enable experimental investigation of the expectation-perception model of auditory hallucinations, a model of auditory predictive coding in healthy, non-hallucinating individuals needs to be formulated. Since neural processes are often reflected in behavioural measures such as reaction time and accuracy (den Ouden et al., 2009), the experimental work described in this thesis aimed to establish behavioural and neural correlates of normal auditory expectation. A design was employed which aimed to induce learning of associations between visual cues and auditory outcomes and subsequently to contrast expected and unexpected auditory events. Participants identified the auditory stimulus, which contained sound or silence (Behavioural Sound/Silence Experiment), or low-or high- pitched sound (Behavioural Pitch Experiment). The perceptual correlates of auditory expectation were also investigated with functional MRI (FMRI Sound/Silence and Pitch Experiments), thought to be more sensitive than behavioural measures (Klucken et al., 2009; Tomasi et al., 2004). The content of auditory hallucinations is often salient (Nayani and David, 1996). In order to elucidate the potential abnormalities in processing of emotionally salient auditory stimuli in those who hallucinate, a model of normal auditory predictive coding of such sounds is needed. Therefore, the aim of the FMRI Salience Experiment was to elucidate the effects of salience on neural processing of expected and unexpected auditory stimuli in healthy volunteers. In this experiment expected neutral words were contrasted with unexpected neutral words and expected salient words were contrasted with unexpected salient words.

### 

# Chapter 2

# Methodology

## Associative learning

Predictive coding can be studied within the associative learning framework. The most influential within this framework is the Rescorla-Wagner [(1972)](#_ENREF_124) model, developed in the context of Pavlovian classical conditioning. While investigating digestion in dogs, Pavlov noticed that the animals salivated before they received food, at the sound of the footsteps of the laboratory assistant who fed them [(Gross, 2005)](#_ENREF_125). This observation led to the development of a conditioning procedure in which a stimulus (a bell) not normally associated with response (salivation) would eventually induce the response by being presented with another stimulus (food), which does produce salivation. Before the conditioning food is called the unconditioned stimulus (US) and salivation the unconditioned response (UR), since salivation is a natural and automatic response to food. After conditioning the bell becomes the conditioned stimulus (CS) since response induced by it is conditional on the pairing of the bell with the US. Salivating induced by CS then becomes the conditioned response (CR). The dog therefore learns association between the two stimuli: the sound of a bell (cue) and the food (outcome), and reacts to the cue by forming an expectation of food, resulting in salivation.

The Rescorla-Wagner rule proposes that the violation of the expectation is essential for learning. The strength of association between the cue (CS) and the second stimulus (US) depends on the prediction error, i.e. the difference between the actual outcome and the prediction, at a given trial. If the outcome (US) is uncertain, the prediction error will be positive and associative strength increases. If the prediction error is zero, i.e. the outcome is completely predicted, associative strength will not change. If the predicted outcome is omitted, the prediction error is negative, and associative strength will be reduced. Learning involves forming a prediction of an event on the basis of all the cues present in the trial and modification of the subsequent prediction on the basis of the prediction error. The Rescorla-Wagner rule applied to neural activity suggests that events that do not match expectation would evoke greater activity in the area that was engaged in learning associations, than events that do match expectation [(Fletcher et al., 2001)](#_ENREF_126). Such increase in activity would be greater for unexpected cue-outcome parings (surprising event) than for unexpected cue-no outcome pairings (surprising omission of an expected event).

## Functional magnetic resonance imaging (fMRI)

Functional magnetic resonance imaging (fMRI) is a method of brain imaging. Magnetic resonance imaging creates images of biological tissue with the use of the static magnetic field, measured in units of Tesla [(Huettel et al., 2009)](#_ENREF_127). The strength of the field varies from 1.5 to 7 Tesla and higher (for comparison, magnets that pull cars out of junkyards have strength of 1 Tesla). A pulse sequence, consisting of changing magnetic gradients and oscillating electromagnetic fields, is employed in order to emit electromagnetic energy. This energy is absorbed by the hydrogen nuclei in the human body. The absorbed energy is then emitted and this released energy is measured and forms the raw MR signal. When placed in a magnetic field, protons will precess (spin in such a way that the rotating axis spins at an angle). In the same magnetic field all protons will spin with the same frequency. As the protons absorb energy, the spins move from the longitudinal to the transverse plane. The release of the absorbed energy – relaxation - has several components: T2 decay as the spins lose coherence, T2\* decay as the normal loss of coherence is combined with differences in precession caused by inhomogeneity of the magnetic field and T1 decay caused by the return of the spins to the longitudinal plane. T1 and T2 vary depending on the type of tissue. In an image based on a T1 contrast white matter will be brightest, gray matter grey and cerebrospinal fluid (CSF) will be darkest. In a T2-weighted image CSF will be brightest (it has the longest T2 relaxation time), gray matter will be gray and white matter will be darkest. Images sensitive to certain properties of the tissue can be created by manipulating the pulse sequence.

Funcitonal MRI uses MRI scanners to image changes in the brain function. The images are based on changes in blood flow which are correlated with activity of neurons. Active neurons have increased metabolic needs and are provided with glucose and oxygen by the vascular system. Oxygen is carried by haemoglobin. Oxygenated haemoglobin is diamagnetic, i.e. it is weakly repulsed by the magnetic field, while deoxygenated haemoglobin is paramagnetic, i.e. it is attracted to the magnetic field. Once oxygen is consumed by neurons, paramagnetic deoxygenated haemoglobin deforms the surrounding magnetic field, i.e. it changes the magnetic field strengths. As a result of this deformation the hydrogen nuclei will precess at different frequencies and T2\* decay will be shorter, resulting in a suppressed MR signal. Deoxygenated haemoglobin is then displaced by oxygenated molecules. Such changes in concentration of oxygen provide blood oxygenation level dependent (BOLD) contrast for fMRI images. Hence,T2\*-weighted images are sensitive to deoxygenated haemoglobin and are the base of the BOLD fMRI.

The BOLD contrast was discovered by Seji Ogawa and colleagues in 1990 [(1990)](#_ENREF_128) and since then fMRI became a very popular method of neuroimaging. The change in MR signal due to neuronal activity is referred to as hemodynamic response. Even though neurons respond to stimulation within tens of milliseconds, the hemodynamic response starts 1-2 seconds later, to achieve maximum at approximately 5 seconds following the stimulation. In case of a prolonged stimulation the peak might extend to a plateau and then decreases to levels below-baseline levels (poststimulus undershoot). It is thought that BOLD reflects the local field potential activity (both excitatory and inhibitory postsynaptic potentials) [(Logothetis et al., 2001)](#_ENREF_129). The main advantage of FMRI is its non-invasiveness and lack of ionising radiation. It addition, it has a high spatial resolution and is widely available [(Huettel et al., 2009)](#_ENREF_127). On the other hand, it is expensive and has relatively poor temporal resolution. The equipment is very claustrophobic and the use of the strong magnetic field precludes participation of those with metal objects inside their body, e.g. pacemakers. In addition fMRI measures neural activity indirectly and interpretation of the positive and negative changes in the BOLD signal is not always straightforward [(Logothetis et al., 2001)](#_ENREF_129). Hence, care needs to be taken in designing studies and choosing statistical analysis procedures in order to take advantages of the considerable potential of fMRI and minimize the disadvantages of the technique.

## Connectivity analysis

Whilst it is important to explore the functional specialisation of regions within the brain, investigating the functional integration adds to the completeness of the neuroimaging research. Functional specialization refers to the specialization of different brain areas for different functions. In terms of neuroimaging it means that activations in these areas can be attributed to specific experimental stimuli [(Friston et al., 1997)](#_ENREF_130). Functional integration, on the other hand, can be defined as interactions between specialized areas or neuronal system and the experimental (sensorimotor or cognitive) conditions. Such functional integration is the object of connectivity models. Connectivity models are based on two approaches: functional and effective connectivity. Functional connectivity is an exploratory, hypothesis-free approach, which focuses on statistical correlations between neurophysiological events in different, often spatially distant regions. It does not attempt to inform of causal directions or underlying mechanisms [(Friston et al., 1993)](#_ENREF_131). Effective connectivity investigates the influence of one neuronal system on another in different experimental condition. It is often based on a priori hypotheses as to how specific areas affect each other. Effective connectivity is equivalent to connection strengths, or synaptic efficacy [(Friston et al., 1997)](#_ENREF_130).

The psychophysiological interactions (PPI), dynamic causal modelling (DCM) and the structural equation modelling (SEM) are connectivity approaches driven by prior hypotheses. Psychophysiological interactions model describes how one neuronal system (physiological measure) influences another neuronal system according to experimental (psychological measure) condition. For instance, one area might modulate activity in another area when the input is ambiguous (Kilian-Hutten et al., 2011). Psychophysiological interactions analysis begins with identifying the seed region of interest (ROI) and a matrix of experimental design. The timeseries extracted from the seed voxel represents the physiological variable, whilst the vector representing the contrast of interest represents the psychological variable (e.g. condition A versus condition B). The PPI regressor is formed by convolving the timeseries of the ROI with the psychological condition vector. The general linear model analysis then searches for brain regions that show changes in connection strength with the seed region depending on experimental manipulation. Such changes are represented by alterations in the strength of correlations between timeseries activity in the seed ROI and other areas. Psychophysiological interactions is an optimal approach if only one ROI is available and the aim of the analysis is to search for areas that are connected with it (Hunter et al., 2010).

In SEM a set of ROIs, i.e. significant activations found in the general linear analysis, is entered into the model. Structural equation modelling tests different models of connections between the seed regions as well as directions of these connections and identifies the model that best fits the timeseries data of the ROIs (Kondo et al., 2004). This type of analysis allows the computation of path models, i.e. statistical methods of investigating interdependencies between the variables. Effective connectivity between the seed ROIs are indicated by the correlations between their timeseries. Optimally several fit measures are selected and combined in order to find the model of the best fit. For instance, the analysis might be employed to investigate how connections between different brain areas contribute to working memory performance.

Dynamic causal modelling is also based on a predefined anatomical network of ROIs. The aim of the analysis is to establish the strengths of connections between the chosen ROIs in different experimental conditions (Friston et al., 2003). Dynamic causal modelling differs from SEM in that it estimates the connectivity on the basis of the neural activity rather than the measured signal (e.g. BOLD) (Penny et al., 2004). One example of an application of such analysis is an investigation whether effects of categories of stimuli in visual cortex are mediated by early visual cortex (bottom-up) or the parietal cortex (top-down) (Mechelli et al., 2003).

## General method and procedure in fMRI experiments (studies: fMRI Sound/Silence, fMRI Pitch and fMRI Salience)

### Participants

The studies were approved by the School of Medicine Research Ethics Committee at the University of Sheffield. Twelve healthy volunteers (6 men) were recruited from the student population of University of Sheffield (mean age 24.33, SD 5.47). All participants were right-handed, as assessed by The Edinburgh Handedness Inventory (Oldfield, 1971). They had no history of psychiatric or neurological disorders and were asked to refrain from drinking coffee or smoking on the day of the scanning. Written informed consent was obtained before commencing the study. Participants’ sociodemographic details were recorded. Subjective auditory acuity, IQ and proneness to hallucinations were assessed using Hearing Handicap Inventory for Adults (Newman et al., 1991), National Adult Reading Test (NART; [Nelson, 1982)](#_ENREF_132) and Launay-Slade Hallucinations Scale-revised [(LSHS; Launay and Slade, 1981)](#_ENREF_133).

### Questionnaires

#### The Endiburgh Handedness Inventory

The Edinburgh Handedness Inventory [(Oldfield, 1971)](#_ENREF_134) measures the hand preference for 10 activities: writing, drawing, throwing, using scissors, using a toothbrush, using a knife, using a spoon, using a broom, striking a match, and opening a box. The responders are instructed to put a ‘+’ sign in the column marked ‘left’ if they use left hand for the given activity, in the column marked ‘right’ if they use right hand. In case of no preference the responders put a ‘+’ sign in both columns. The Inventory has high validity and reliability [(Ransil and Schachter, 1994)](#_ENREF_135). The average score of 92.33 (SD 14.35) indicated that all participants were right-handed.

#### Hearing Handicap Inventory for Adults

The Hearing Handicap Inventory for Adults (Newman et al., 1991) consists of 25 items concerned with social (12 items) and emotional (13 items) aspects of potential hearing loss, e.g. ‘Does a hearing problem cause you to use the phone less often than you would like?’. Responses include ‘yes’, ‘no’ and ‘sometimes’. Scores can range from 0 (no handicap) to 100 (maximum handicap), with high scores suggesting a hearing problem. The Hearing Handicap Inventory for Adults has a high test-retest reliability [(Newman et al., 1991)](#_ENREF_136) and scores are associated with pure-tone sensitivity and supra-threshold word recognition ability [(Newman et al., 1990)](#_ENREF_137). The average score was 2 (SD 3.07).

#### National Adult Reading Test (NART)

National Adult Reading Test [(Nelson, 1982)](#_ENREF_132) assesses pronunciation of 50 irregularly pronounced English words in order of increasing difficulty, e.g. simile, topiary. It is untimed and scored by summing up the number of words pronounced correctly. The test has high construct validity and as a measure of general IQ and high reliability [(Crawford et al., 1989)](#_ENREF_138). The number of errors in NART predicts the Wechsler Adult Intelligence Scale –revised (WAIS-R) score [(Wechsler, 1981)](#_ENREF_139). The mean WAIS-R full scale IQ in the current study predicted from NART was 116.8 (SD 3.9). Two participants could not be assessed using NART due to their experience with administering the test.

#### Launay-Slade Hallucinations Scale -revised

The Launay-Slade Hallucinations Scale (LSHS)-revised is a self-report scale assessing predisposition for hallucinations (Launay and Slade, 1981, Bentall and Slade, 1985). It consists of 12 items, e.g. ‘I often hear a voice speaking my thoughts aloud’. The LSHS has high test-retest reliability on healthy male participants with the mean 19.35 (SD 7.27) [(Bentall and Slade, 1985)](#_ENREF_140). It contains 4 subscales divided into those corresponding to clinical traits (auditory hallucinations, visual hallucinations) and sub-clinical features (vivid thoughts and intrusive thoughts, vivid daydreams) [(Levitan et al., 1996)](#_ENREF_141). Responses are measured on the scale: certainly does not apply, possibly does not apply, unsure, possibly applies, certainly applies. It is scored by adding the ratings, which can range from 0 to 48. The greater the score, the higher predisposition for hallucinations. The mean score on LSHS in this study was 11.58 (SD 8.8). Some of the items corresponding to auditory hallucinations endorsed by healthy participants in Bental and Slade [(1985)](#_ENREF_140) were also scored as possibly or certainly applying to themselves by two participants in this study.

### Procedure

Participants were asked to read the information sheet and were invited to sign the consent form. They then proceeded to fill the questionnaires. The experiments consisted of two phases: acquisition of contingencies and mismatch. In the acquisition phase participants completed acquisition stage of fMRI Sound/Silence Experiment followed by acquisition stage of fMRI Pitch Experiment, followed by acquisition stage of fMRI Salience Experiment. This stage took approximately 30 minutes. In the mismatch phase participants completed the mismatch phase of fMRI Sound/Silence experiment, followed by the mismatch phase of fMRI Pitch experiment and the mismatch phase of fMRI Salience experiment. Each stage of the mismatch phase was preceded by a refresher lasting approximately 5 minutes, which reminded the participants the contingencies acquired in the acquisition stage. The scanning lasted approximately 1hour 15 minutes. The order of the procedures was based on the results of the Behavioural Sound/Silence and Pitch Experiments (Chapter 2). The difference in response time between unexpected and expected silences and sounds in Behavioural Sound/Silence Experiment was greater than the difference in the response time between unexpected and expected low- and high-pitched sounds in Behavioural Pitch Experiment. Since fMRI Sound/Silence Experiment employed the same auditory outcomes as Behavioural Sound/Silence Experiment, participants completed it first in order to increase chance of finding the difference between unexpected and expected auditory stimuli.

Each participant was scanned at 3 T (Achieva 3.0T, Philips Medical Systems, Best, NL) at the University of Sheffield. Functional data for each participant was obtained using aT2\*-weighted, echo-planar (EPI) imaging sequence in 3 functional runs lasting 14.47 minutes each. Each functional run provided 69 volumes. Each volume consisted of 35 cranio-caudal, 4 mm-thick slices, covering the whole brain (acquisition time was 3000 ms, echo time = 45 ms and repetition time = 12500 ms, matrix 128x128, field of view 240 mm).

### Scanning

In order to control for the effects of the scanner noise, a sparse protocol was used [(Hall et al., 1999)](#_ENREF_142) (Figure 2.1). This protocol takes advantage of the delay in the haemondynamic response peak (6-7s) to an auditory stimulus. The MR excitation started 3 seconds after the onset of the auditory stimulus and lasted 3 seconds, allowing for brain volume imaging near the peak of the haemodynamic response to the experimental stimulus (Figure 2.1). Thirty five image slices were then acquired covering the entire brain. The imaging of the next auditory stimulus was presented 9.5 s later, after the haemodynamic response to the MRI- associated gradient-switching noise had time to decay. Such delay allowed to reduce the interference between scanner noise- evoked and experimental-stimulus-evoked auditory response (Lewis-Hannah et al., 2011).

500ms

500ms

500ms

750ms

500ms

2500ms

3000ms

4250ms

imaging



**Figure 2.1: The scanning time course.**

### Data preprocessing

Data were analysed using SPM5 software ([www.fil.ion.ucl.ac.uk/spm](http://www.sciencedirect.com/science?_ob=RedirectURL&_method=externObjLink&_locator=url&_issn=10538119&_origin=article&_zone=art_page&_plusSign=%2B&_targetURL=http%253A%252F%252Fwww.fil.ion.ucl.ac.uk%252Fspm)). Each participant’s images were slice-time corrected to the middle slice. Correction for head movement was performed and the resultant images were realigned to the mean of all realigned images. Images were normalized to the Montreal Neurological Institute (MNI) space (echo-planar template in SPM-5) and smoothed with an 8 mm full-width at half-maximum Gaussian kernel.

# Chapter 3

# Behavioural correlates of expectation of auditory stimuli

**Abstract**

Normal perception relies on the process of predictive coding, in which neural networks establish regularities among the perceived stimuli. We propose that disturbances in predictive coding, and specifically in processing of unexpected stimuli, underlie the formation of auditory hallucinations. In the studies described in this chapter, we investigated normal mechanisms of auditory predictive coding. Sixty participants completed each of the tasks, consisting of pairs of associated stimuli. When cued by the visual stimulus, participants indicated whether the auditory stimulus in the current trial was sound or silence (Behavioural Sound/Silence Experiment) or high- or low-pitched sound (Behavioural Pitch Experiment). Whilst the majority of the auditory stimuli were presented within the learnt associations (i.e. they were ‘expected’), the minority appeared in unexpected configurations (i.e. ‘unexpected’). We hypothesised that unexpected auditory stimuli would be associated with longer response time and decreased accuracy compared with their expected counterparts. Response time and accuracy were recorded.

Results revealed a trend-level increase in response time to unexpected, compared with expected, auditory stimuli in Behavioural Sound/Silence Experiment. There was a trend towards greater accuracy in responding to unexpected sounds than when responding to expected sounds and towards decreased accuracy when responding to unexpected silence, compared with expected silence. In the Behavioural Pitch Experiment response time to sounds of expected and unexpected pitch was similar. Participants were significantly more accurate when responding to unexpected low-pitched, compared with expected low-pitched tones. These results suggest that the relationship between behavioural measures and auditory expectations might depend on the characteristics of the auditory stimuli in relation to each other.

## 3.1. Introduction

The efficiency of normal perception is achieved through the process referred to as predictive coding, in which neural networks establish patterns between perceived events (Rao and Ballard, 1999, Winkler, 2007). This process allows to predict what is likely to occur in the environment and to form predictive representations of the incoming stimuli [(Summerfield and Egner, 2009)](#_ENREF_75). Such predictive representations reduce the computational effort [(Rao and Ballard, 1999)](#_ENREF_1). ‘Higher’ brain areas send predictions of incoming signal to ‘lower’ areas. In turn, ‘lower’ areas inform ‘higher’ areas of the differences between the top-down prediction and bottom-up input, i.e. they generate prediction errors.

Evidence suggests that processing events that deviate from the implicit knowledge about relationships between them affects response time and accuracy. For instance, when presented with pairs of words, participants were quicker and more accurate in responding to words that are associated (such as ‘bread-butter’ or ‘doctor-nurse’) than words that are not associated (e.g. ‘bread-doctor’ or ‘nurse-butter’) [(Meyer and Schvaneveldt, 1971)](#_ENREF_143). Auditory expectation can also be formed by priming [(Bharucha and Stoeckig, 1986)](#_ENREF_144). Target chords harmonically related to preceding prime chords were identified more quickly and accurately than target chords preceded by harmonically unrelated chords.Similarly, expectation of an upcoming tone sequence develops through exposure to such structures [(Tillmann and Poulin-Charronnat, 2010)](#_ENREF_145). Here, expectation was reflected in quicker and more accurate detection of target tones that respected the learned rules than target tones that did not respect the rules.

Such implicit, natural associations can be replaced with sequences of events, where spoken phonemes follow pictures of sign-language gestures corresponding to these phonemes [(Aleksandrov et al., 2010)](#_ENREF_146). Sounds presented within the learned pairs were associated with faster and more accurate responses, compared with sounds presented outside of learned pairs. When high or low beeps predicted visual stimuli (houses and faces), participants were quicker and more accurate at responding to predictable, compared to unexpected, stimuli [(den Ouden et al., 2010)](#_ENREF_147). Finally, Correa and colleagues (2005) showed that responses to targets (visual letters) which followed temporally valid cues (shapes) were quicker than responses to targets which followed invalid cues. Here, targets cued correctly corresponded to expected outcomes, whilst those cued incorrectly to unexpected outcomes. The decrease in response time was accompanied by increase in perceptual sensitivity, suggesting expectancy enhances not only the motor response but also the perceptual processing.

While most of the existing studies, employing language or music stimuli, are concerned with learning of structure of complex systems, this study will attempt to induce implicit learning by employing simple visual and auditory stimuli. One of the models that can be employed to investigate the processing of prediction error in predictive coding is the Rescorla –Wagner model of associative learning (1972, Schultz and Dickinson, 2000) (refer to Chapter 2, Section 1). This model suggests that once the association between a cue and the cued outcome has been learnt, unexpected outcomes produce an error signal that changes the strength of the subsequent associations between the stimuli (cue and outcome) and hence, future expectation.

We propose that associative learning plays a vital role in the formation of auditory hallucinations. Specifically, ‘voices’ can be generated during the process of association of auditory perceptions with certain activities and emotions. For instance, eating might be associated with a heard derisive commentary, which evokes low mood and feelings of threat. As a result, eating and low mood could then act as cues for the stored perception of negative commentary. The impaired processing of prediction error seen in schizophrenia (Umbricht et al., 2006) may reduce the influence of the (contradictory) external input in modifying the prediction, thus allowing abnormal auditory expectation to prevail. Such misconstruing of internal sensory representation may thus lead to heard perceptions in the absence of external input.

### 3.1.1 Aims

It is plausible that auditory hallucinations occur when reduced generation and processing of prediction error allows the expectation of sound to prevail even when no sound is occurring (an ‘unexpected omission’ in associative learning terminology) or when external input consists of another sound (‘unexpected events’). We therefore employed behavioural measures to examine the process of auditory predictive coding in healthy individuals. Specifically, we aimed to elucidate how violations of expectation, including both unexpected events and omissions, affect response time and accuracy. We developed an associative learning task consisting of pairs of stimuli and contrasted conditions of expected and unexpected sounds and silences and low- and high-pitched tones.

The implicit nature of induced learning is important because it is thought to underlie the perception of particular stimuli in auditory hallucinations. The associations of visual and auditory stimuli can serve as a model for the development of internal associations, which underlie auditory hallucinations. The simplicity of the stimuli will allow to pinpoint the basic perceptual processes.

## 3.2. Paradigm development

The pairs of associated stimuli were composed of visual and auditory items. The first design of the behavioural task involved a square followed by a tone and a triangle followed by silence (see Figure 3.1 a). The shapes were presented for 500 ms. After a gap of 250 ms followed either 500ms tone or silence. The task was to respond to the auditory events by pressing the right arrow key on the keyboard if the trial contained a sound and the left arrow key when the trial contained silence. In this design, however, it would be possible for participants to ignore the shapes and focus on the auditory stimuli, and thus not learn the associations between the shapes and sounds. On the other hand, if participants were watching the shapes and learning the associations, they would be able to prepare their response and press the response key before the sound arrived, thus rendering the analysis of response time meaningless.

In the subsequent version of the task the visual and auditory stimuli were presented simultaneously (see Figure 3.1.b). Participants were to respond by pressing the right arrow key on the keyboard if the shape was a square and the left arrow key if it was a triangle. However, while this design would ensure that participants registered the shapes, it was possible that the auditory events would cue the response, e.g. a tone would serve as a signal to press the right arrow key for a square. In addition, simultaneous presentation of the shapes and sounds would make it impossible to determine whether the visual stimulus cued the auditory event or vice versa.

In the third attempt to design the paradigm the visual and auditory stimuli were dissociated in time, i.e. the square was followed by a tone and the triangle was followed by silence (see 3.1c). Simultaneously with auditory events, a triangle and a square appeared in either left or right corner of the screen. Instructions in this version of the task were to press the right arrow key if the shape that corresponded to the previously seen figure was in the right corner of the screen, and the left arrow key if the shape that corresponded to the previously seen figure was in the left corner of the screen. The presence of the response-cuing shapes ensured that participants would register the shapes and thus learn the associations. The randomized position of the response-cuing shapes on the screen would prevent the set response pattern, e.g. where a tone would serve as a signal to press the arrow key for a square and silence as signal to press the arrow key for a triangle. However, it was still possible that the auditory events would cue the response to a particular shape.

The final version of the behavioural paradigm resolved the problems presented by previous designs (Figure 3.2). The shapes and sounds were dissociated in time, ensuring that the visual stimuli cued the auditory events. Following the first presentation of a shape, a pair of shapes cued the response to the square or triangle, ensuring that the visual stimuli were registered, thus making it more likely that participants would learn associations between the stimuli. The response to subsequent auditory events was cued by the words ‘sound/ silence’ presented on the screen. The position of the words on the screen and hence response keys was randomized so that the effect of expectation on response time would not be due to visual stimuli cuing response with right finger or the left finger. Therefore, the paradigm was considerably less liable than its previous versions to different strategies employed by participants. The task required sustained concentration and participants were not informed about the associations in order to make the task as ecological as possible. Using familiar auditory stimuli as unexpected outcomes allows to avoid confounding unexpectedness with unfamiliarity.

## 3.3. Behavioural Sound/Silence Experiment. Silence substituted with sound

### 3.3.1 Aims

We propose that auditory hallucinations occur when prediction error is reduced and the auditory expectation of sound prevails over the external stimuli. Such enhanced role of prediction in shaping the final percept could occur even in the absence of sound (an ‘unexpected omission’) or when external input consists of another sound (‘unexpected events’). The aim of the Behavioural Sound/Silence Experiment was to examine the predictive coding mechanisms in healthy individuals. In particular, we investigated how unexpected events (when silence is expected) and unexpected omissions (when a sound is expected but does not occur) affect response time and accuracy in healthy individuals.

## 3.3.2. Hypotheses

It was hypothesised that the response time and accuracy depend on auditory expectation. Specifically, once participants learn associations between the visual and auditory stimuli, the response time to auditory items that violate the learned expectation would be longer and accuracy would be lower than the response time and accuracy to those items that match expectation. The hypothesised processes underlying the effect of longer response time to unexpected outcomes involve cuing sensory representations of upcoming auditory stimuli and priming sensory cortex for the auditory stimuli and response required. Specifically, as a result of repetitive presentation of a triangle paired with silence, the processing of the triangle by visual cortex could lead to retrieval of the representation of silence in the auditory cortex. The representation of the input could be retrieved before the actual auditory stimulus



500 ms

250 ms

500 ms

500 ms

250 ms

500 ms



Silence

Tone

**a**



500 ms

500 ms



Silence

Tone

**b**



500 ms

250 ms

500 ms

250 ms

500 ms



Silence

Tone

**c**

**Figure 3.1. The mismatch phase in the initial versions of the behavioural paradigm.** a) First design b) Second design c) Third design.

arrived, reflecting formation of ‘a cortical model of what will happen next’ [(Hughes et al., 2001)](#_ENREF_148). If indeed no sound was presented, the silence would be rapidly communicated to the visual and motor cortex, facilitating the response cued by the printed word ‘silence’ (a situation of expected silence). If the outcome was sound (unexpected sound), more neuronal resources in the auditory cortex would have to be directed to analysis of input, and the increased computational burden would slow down the communication from the auditory to the visual and motor cortex, resulting in longer response time and lower accuracy. Processing of the square could evoke an auditory representation of the sound before the input arrived. If the sound was presented, it would be rapidly communicated to the visual and motor cortex, facilitating response cued by the printed word ‘sound’ (condition of expected sound). If the outcome instead was silence (unexpected silence), increased computational burden could affect behavioural response.

**Hypothesis 1)** predicted that participants would respond more quickly to sound than to silence. There would be no difference in accuracy between responses to sounds and silence.

**Hypothesis 2)** stated that, following the visual cue, an unexpected silence (i.e. silence following a cue which had previously been associated with sound) would be associated with a longer response time and lower accuracy than an expected silence.

**Hypothesis 3)** predicted that unexpected sounds (i.e. sounds following a cue which had been associated with silence) would be associated with a longer response and lower accuracy than expected sounds.

### 3.3.3. Method

The study was approved by the School of Medicine Research Ethics Committee at the University of Sheffield.

#### 3.3.3.1. Participants

Sixty healthy adult volunteers (35 females, 25 males, mean age 27.7, SD 5.57) were recruited from university notice board advertisements and mailing lists. A note of participants’ gender, age and handedness was recorded, anonymised and stored in compliance with the Data Protection Act.

#### 3.3.3.2. Stimuli

Stimuli were presented in the commercially available Presentation’ software (Neurobehavioral Systems, Albany, USA, www.neurobs.com) on a computer (Toshiba M30, screen size 15”). Shapes included a white, unfilled square and a white, unfilled triangle presented on the black screen. Words ‘silence/sound’ were printed in white font on the black screen. A 440 Hz tone was created in open source software (Audacity: www.audacity.sourceforge.net). Sounds were delivered via headphones (Sennheiser HD 202).

#### 3.3.3.3. Procedure

The study took place in a quiet room in order to avoid distractions. Participants were presented with an information sheet and invited to sign a consent form. Participants were asked to respond to the stimuli as quickly and as accurately as possible. Behavioural Sound/Silence Experiment consisted of two phases: acquisition and mismatch. Fifteen to twenty trials conforming to the contingency is sufficient to induce learning of complex rules (Bendixen et al., 2008). In Meyer and colleagues’ study (1971) 12 participants performed a task consisting of 48 pairs of associated words (expected) and 48 pairs of unassociated words (unexpected trials). Here participants did not have to learn the associations, which were embedded in their implicit language knowledge. Correa and colleagues (2005) employed a between-participants design, in which the experiment consisted of 6 conditions and was completed by 40 participants. Out of the 150 trials (divided into blocks) 50 contained targets following invalid cues (unexpected). In the current study each task was completed by 60 participants, who had to learn the associations between the stimuli. In order to maintain the unexpected nature of the stimuli, it was important to reduce the number of unexpected associations to 20% of all the trials. Since the number of participants in the current study was relatively high, the design was within-participants and consisted of four conditions and the task required high level of concentration, the number of trials was reduced. Our power calculations indicated that 60 trials, including 10 unexpected, would be sufficient.

**Acquisition phase**

Acquisition phase was preceded by a practice session to ensure that participants understood the instructions. This phase aimed to induce learning of associations. Unbeknownst to the participants, a triangle was always followed by silence (30 trials) and a square was always followed by tone (30 trials) (see Figure 3.2). The order of the trials was randomized. First, one of the shapes (a triangle or a square) was presented on the screen, followed, after a 500ms gap, by both shapes side-by side. Participants indicated whether the initially presented shape appeared on the left or the right from the centre of the screen. Following a further 500ms pause the words ‘sound’ and ‘silence’ appeared on the screen side by side accompanied by either the presence or the absence of an auditory stimulus. Participants were required to indicate whether the text describing the actual auditory stimulation appeared on the left or the right from the centre of the screen. This stage took approximately 5 minutes.

**Mismatch phase**

In the mismatch phase expected silences and sounds (80% of trials) were contrasted with unexpected silences and sounds (20% of trials). Therefore, the mismatch phase consisted of 25 pairs of triangle-silence (expected silences), 25 pairs of square-sound (expected sounds), 5 pairs square-silence (unexpected silences) and 5 pairs of triangle-sound (unexpected sounds). The 20% was chosen in order to maintain the unexpected nature of the stimuli [(den Ouden et al., 2009)](#_ENREF_14) and at the same time provide sufficient statistical power in comparing response time to expected and unexpected outcomes. The order of the trials in the mismatch phase was pseudo-randomized so that unexpected outcomes did not appear in the first 10 trials and that mismatched trials were separated from each other by at least 3 matching trials. Such spacing of the trials containing unexpected outcomes allowed to maintain the unexpected nature of the auditory stimuli in the mismatched trials. Measuring the accuracy rate in the training stage in identifying both shapes and sounds enabled psychophysical validation of the stimuli. This phase lasted approximately 5 minutes.

sound silence



500 ms

500 ms

Until response detected

Until response detected

Until response detected

500 ms

500 ms

Until response detected

500 ms



500 ms

sound silence

Silence

Tone

**Figure 3.2. Task design in acquisition phase (Behavioural Sound/Silence Experiment), designed to induce learning of the associations.** Participants responded to both visual and auditory stimuli. Response to the shape was cued by the pair of shapes in the centre of the screen. The triangle and the square appeared simultaneously and remained on the screen until response was detected. Participant responded to them by pressing right arrow key if the shape on the right from the centre of the screen corresponded to the previously presented single shape and the left arrow key if the shape on the left from the centre of the screen corresponded to the previously presented single shape. Response to the sound was cued by words ‘sound’ and ‘silence’ appearing in the centre of the screen simultaneously with auditory events until response was recorded. Participants pressed the right arrow key when the word on the right from the centre of the screen corresponded to what they heard and the left arrow key if the word on the left from the centre of the screen corresponded to what they heard. Position of the shapes and words on the screen was randomized.

### 3.3.4. Results

Response time in tens of milliseconds (from the start of stimulus presentation to the keypress) to both visual and auditory stimuli was recorded and converted into milliseconds (Table 3.1). Accuracy of responses to both shapes and sounds was determined as percentages of total number of trials (Table 3.2). Response time for incorrect responses was excluded from the analysis.

A within-sample t-test revealed that there was no significant difference in the response time to the triangles (mean 502.5, SD 101.61 ms) and the squares (mean 508.14, SD 113.07), t (59)=1.22, p=0.23). Wilcoxon signed-ranks test revealed that accuracy of responses to triangles (median 100, range 13.33) and squares (median 100, range 16.67) was also similar (z=-0.43, p=0.67).

**Table 3.1. Mean response time (and SD) in milliseconds to auditory stimuli in the mismatch phase.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Silence** | **Sound** | **Overall** |
| **Expected** | 977.99 (218.78) | 909.99 (196.55) | 944.58 (202.57) |
| **Unexpected** | 1017.77 (230.23) | 916.59 (220.9) | 967.59 (208.58) |
| **Overall** | 997.88 (224.51) | 913.29 (208.73) |  |

Repeated measures 2 (expectation: low and high) by 2 (stimulus: silence and sound) ANOVA showed that there was a trend towards longer response time to unexpected, compared with expected, auditory stimuli (F(1, 59) =2.88, p=0.095). Participants were significantly quicker when responding to sound than when responding to silence, F(1, 59) = 33.88, p<0.001). There was no significant interaction between expectation and stimulus (F(1, 59) = 2.11, p=0.15).

**Table 3.2. Mean accuracy (and SD) in percentage of responses to auditory stimuli in the mismatch phase.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Silence** | **Sound** | **Overall** |
| **Expected** | 97.6 (3.05) | 95.67 (5.6) | 96.64 (4.33) |
| **Unexpected** | 95.33 (11.27) | 97.0 (8.09) | 96.17 (9.68) |
| **Overall** | 96.47 (7.16) | 96.34 (6.85) |  |

Repeated measures 2 (expectation: low and high) by 2 (stimulus: silence and sound) ANOVA showed that there was no significant difference in accuracy between responses to expected and unexpected auditory stimuli, F (1,59)=0.37, p=0.55). Accuracy of responses to silences and sounds was also similar, F (1,59)=0.02, p=0.89). An interaction effect approached significance (F(1,59)=3.5, p=0.07), such that there was a trend towards greater accuracy in responding to unexpected sound than when responding to expected sound, and decreased accuracy when responding to unexpected silence, compared with expected silence.

### 3.3.5. Discussion

This study investigated the effect of expected and unexpected stimuli on response time and accuracy as behavioural measures of cognitive processing. In particular, the study attempted to determine how processing of unexpected stimuli depends on the type of learned associations (a visual stimulus followed by sound or silence). The results revealed a trend towards longer response time to unexpected, compared with expected, silences and sounds. This effect was in the direction predicted by the hypothesis. The observation that participants responded to silences significantly more slowly than to sounds may reflect the need to actively determine the absence of sound in silence conditions. The trend for more errors in responding to unexpected, compared with expected, silences was also in the hypothesised direction. The trend for fewer errors in responding to unexpected, compared with expected sounds was in the opposite direction to that hypothesised. It appears that when participants expected a sound and heard silence instead, they were more prone to respond as if the auditory stimulus was a sound. This trend suggests that the visual cue could have evoked a representation of the sound, which might have affected behavioural response. On the other hand, a trend for greater accuracy in responding to unexpected sounds than to expected sounds suggests that participants might have formed a representation of silence. When instead of silence they heard a sound, the sound could have displaced the representation of silence relatively easily. Here, a startling effect could trigger enhanced concentration and performance. Such attention-attracting effect of sounds presented when silence was expected could also cancel out the potential increase in response latency that might have been associated with unexpectedness and thus reduce the effect of expectation on response time.

These trend-level results can be only tentatively interpreted as suggesting that expectation might have affected responses to auditory stimuli. Results of other studies have shown that participants responded more quickly to target chords that were harmonically primed by preceding prime chords, compared with chords that were not primed [(Bharucha and Stoeckig, 1986)](#_ENREF_144). Similarly, tone sequences that deviate from the learned rules were associated with longer response time that sequences that followed rules [(Tillmann and Poulin-Charronnat, 2010)](#_ENREF_145). In studies investigating language, participants responded more quickly and more accurately to spoken phonemes presented within previously learned associations, compared with those presented outside of those associations [(Aleksandrov et al., 2010)](#_ENREF_146).

## 3.4. Behavioural Pitch Experiment: sound substituted with another sound

### 3.4.1 Aims

The expectation-perception hypothesis of auditory hallucinations proposes that the ‘voices’ occur when reduced auditory prediction error does not allow for the modification of the expectation in accordance with the external input. As a result, a bottom-up signal could be interpreted as that confirming the prediction and consequently, misconstrued as a real sound. The aim of the Behavioural Pitch Experiment was to elucidate the mechanisms of auditory predictive coding in healthy individuals. Specifically, we examined how sounds of unexpected pitch (‘unexpected events’ in the associative learning terminology) affect response time and accuracy in healthy individuals.

## 3.4.2. Hypotheses

It was hypothesised that auditory expectation with influence the response time and accuracy. In particular, once participants learn associations between the visual and auditory stimuli, the response time to auditory items that violate the learned expectation would be longer and accuracy would be lower than the response time and accuracy to those items that match expectation.

**Hypothesis 1)** stated that there would be no difference in accuracy or reaction time between sounds of low and high pitch.

**Hypothesis 2)** stated that unexpected low-pitched sounds (i.e. low-pitched sounds following a cue which had previously been associated with high-pitched sounds) would be associated with longer response time and lower accuracy than expected low-pitched sounds.

**Hypothesis 3)** predicted that unexpected high-pitched sounds (i.e. high-pitched sounds following a cue which had previously been associated with low-pitched sounds) would be associated with longer response time and lower accuracy than expected high-pitched sounds.

### 3.4.3. Method

The study was approved by the School of Medicine Research Ethics Committee at the University of Sheffield.

#### 3.4.3.1. Participants

Sixty healthy adult volunteers (25 females, 35 males, mean age 25.57, SD 6.6) were recruited from the university notice board advertisements and mailing lists. A note of participants’ gender, age and handedness was recorded, anonymised and stored in compliance with the Data Protection Act.

#### 3.4.3.2. Stimuli

Stimuli were presented in the commercially available ‘Presentation’ software (Neurobehavioral Systems, Albany, USA, www.neurobs.com). Shapes included a white, unfilled triangle and a white, unfilled square presented on the black screen. Words ‘low/high’ were printed in white 28 font on the black screen. Sounds were created in the open source software (Audacity: www.audacity.sourceforge.net) and included a 110 Hz tone (low pitch) and a 880 Hz tone (high pitch).

#### 3.4.3.3. Procedure

Behavioural Pitch Experiment was completed in a quiet room and consisted of two phases: acquisition and mismatch.

**Acquisition phase**

This phase aimed to induce learning of the associations between the visual and the auditory stimuli. The acquisition phase was preceded by a short practice to ensure that participants understood the instructions. A square was followed by a low-pitched tone (30 trials) and a triangle by a high-pitched tone (30 trials) (see Figure 3.3). Participants were not informed of this rule. They were first presented with a single shape (either a square or a triangle), followed by a 500 ms pause (blank screen) and then both shapes side-by-sides. They responded by indicating whether the previously seen single shape was on the right or on the left side from the centre of the screen. This was followed by another 500 ms pause and words ‘low’ and ‘high’ were presented on the screen, accompanied by either a low- or a high-pitched sound. Participants indicated whether the word corresponding to the auditory stimulus was on the right or left from the centre of the screen. The order of the trials was randomized. This stage took approximately 5 minutes.

low high



500 ms

500 ms

Until response detected

Until response detected

Until response detected

500 ms

500 ms

Until response detected

500 ms



500 ms

low high

Low-pitched tone

High-pitched tone

**Figure 3.3. Task design in acquisition phase**. Participants responded to both visual and auditory stimuli. Response to the shape was cued by the pair of shapes in the centre of the screen. The triangle and square appeared simultaneously and remained on the screen until response was detected. Participant responded to them by pressing right arrow key if the shape on the right from the centre of the screen corresponded to the previously presented single shape and the left arrow key if the shape on the left from the centre of the screen corresponded to previously presented single shape. Response to the sound was cued by words ‘low’ and ‘high’ appearing in the centre of the screen simultaneously with auditory events until response was recorded. Participants pressed the right arrow key when the word on the right from the centre of the screen corresponded to what they heard and the left arrow key if the word on the left from the centre of the screen corresponded to what they heard. Position of the shapes and words on the screen was randomized.

**Mismatch phase**

In the mismatch phase 20% of trials were unexpected: 5 pairs of square followed by a high-pitched tone (unexpected high-pitched tone) and 5 pairs of a triangle followed by a low-pitched tone (unexpected low-pitched tone). The remaining trials consisted of 25 pairs: a square followed by a low-pitched tone and 25 pairs: a triangle followed by a high-pitched tone. Randomly alternating response keys prevented participants from preparing the response with the right or left finger. Responding to both shapes and sounds ensured that participants were paying attention to the stimuli. The order of the trials in the mismatch phase was pseudo-randomized so that that unexpected tones did not appear in the first 10 trials and that mismatched trials were separated from each other by at least 3 matching trials. In order to ensure that participants correctly differentiated between the stimuli, response time and accuracy in the acquisition phase were recorded. This phase lasted approximately 5 minutes.

### 3.4.4. Results

Response time in tens of milliseconds (from the start of stimulus presentation to the keypress) to both visual and auditory stimuli were recorded and converted into milliseconds (Table 3.3). Accuracy of responses to both shapes and sounds was determined as percentages of total numbers of stimuli (Table 3.4). Times for the incorrect responses were excluded.

A Wilcoxon signed-ranks test revealed that there was no significant difference between the response time to triangles (median 465.62, range 544.21) and squares (median 462.07, range 514.13), z=-0.54, p=0.59. Accuracy of responses to triangles (median 100, range 36.67) and squares (median 100, range 33.33) was also similar, z=0.89, p=0.2.

**Table 3.3. Mean response time (and SD) in milliseconds to auditory stimuli in the mismatch phase.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Low pitch** | **High pitch** | **Overall mean** |
| **Expected** | 883.03 (249. 04) | 881. 79 (282. 17) | 882.41 |
| **Unexpected** | 898. 74 (310. 76) | 881. 37 (278.04) | 890.06 |
| **Overall mean** | 890.89 (279.9) | 991.58 (280.11) |  |

Repeated measures 2 (expectation: low and high) by 2 (pitch: low and high) ANOVA showed that response time to expected stimuli did not significantly differ from response time to unexpected stimuli, F(1, 59) =0.35, p=0.56. Neither did response time to low-pitched tones differ significantly from response time to high- pitched tones, F(1,59) = 0.33, p=0.57. There was no significant interaction between expectation and pitch F(1, 59)=0.3, p=0.59).

**Table 3.4. Mean accuracy (and SD) in percentage of responses to auditory stimuli in the mismatch phase.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Low pitch** | **High pitch** | **Overall** |
| **Expected** | 96.07 (5.82) | 96.4 (4.21) | 96.24 (5.02) |
| **Unexpected** | 98.00 (6.05) | 95.67 (9.09) | 96.84 (7.57) |
| **Overall** | 97.04 (5.54) | 96.04 (6.65) |  |

Repeated measures ANOVA 2 (expectation: high and low) by 2 (stimulus: low and high pitch) revealed no main effect of expectation on accuracy (F (1,59)=0.62, p=0.43). Accuracy of responses to low-and high-pitched tones was also similar (F(1.59)=1.15, p=0.29). There was a significant interaction between expectation and stimulus type such that participants were significantly more accurate responding to unexpected low-pitched, compared with expected low-pitched tones, F(1.59)=5.22, p=0.026.

### 3.4.5. Discussion

This study investigated the effect of expected and unexpected sounds of different pitch on response time and accuracy as indirect measures of cognitive processing. There was no significant difference in response time between expected and unexpected low-and high-pitched sounds. This result was not in line with the hypothesis, which stated that participants would be significantly quicker in responding to expected, compared with unexpected, sounds. As predicted, participants responded with similar latency and accuracy to low-and high-pitched sounds. Contrary to the hypothesis, which predicted reduced accuracy in responding to unexpected, compared with expected, sounds, participants were more accurate in responding to unexpected low-pitched sounds than to expected low-pitched sounds.

The lack of difference in response time between sounds of expected and unexpected pitch could be interpreted as indicating that participants failed to form cortical representations of high- or low-pitched sounds following visual cues. However, the increased accuracy in response to unexpected, compared with expected, low-pitched sounds, suggest that when participants formed a representation of a high-pitched sound, the low-pitched sound presented instead could have an attention-grabbing effect. The stronger effect of the auditory representation of a high-pitched, relative to the low-pitched, tone, could be due to greater urgency of high-pitched sounds, often used as alarms and warnings [(Hellier and Edworthy, 1999)](#_ENREF_150).

Hence, results of the current study differed from the results of the priming studies, in which primed chords and tone sequences that respected rules were associated with faster and more accurate responses than chords that were not primed and tone sequences that violated rules (Bharucha and Stoeckig, 1986, Tillmann and Poulin-Charronnat, 2010). It might be that processing of auditory stimuli in the context of complex systems such music and speech, involves more cognitive and more complex processes and greater brain areas. As a result, predictive representations of sounds in the auditory cortex are stronger and have a greater effect on behaviour than representations of sounds not embedded in a language or music system. This explanation might relate to the results of Aleksandrov and colleagues study [(2010)](#_ENREF_146), in which participants were slower and less accurate in responding to unexpected spoken phonemes that were associated with corresponding sign-language gestures, but not when they were associated with geometrical figures. Alternatively, it could be that insufficient strength of auditory representations in this study was due to the inadequate contrast between the low and high pitch of the tones.

## 3.5. General discussion (Behavioural Sound/Silence and Pitch Experiments)

The studies presented in this chapter investigated the effect of expected and unexpected auditory stimuli on the response time and accuracy as measures of cognitive processing. In particular, we investigated processing of unexpected presence and unexpected absence of sound, and the more subtle perceptual mechanisms associated with sounds of unexpected pitch.

Associative learning is suitable for investigating the mechanisms of predictive coding, a process of learning patterns between stimuli by neural networks (Rao and Ballard, 1999, Winkler, 2007). Such learning allows to form expectations of external events and thus reduce the neural resources needed to process these stimuli. Expectations are modified when ‘lower’ cortical areas send a prediction error signal – the difference between the external stimulus and the expectation. The expectation-perception model of auditory hallucinations presented in this thesis proposes that the ‘voices’ arise as a result of abnormalities in the auditory predictive coding. Specifically, reduction of the prediction error found in schizophrenia (Umbricht et al., 2006, Fisher et al., 2012) leads to insufficient updating of the expectation in the face of the external input. As a result, the prediction could be misconstrued as a signal corresponding to an external stimulus and form an auditory hallucination.

The results of the studies described in this chapter revealed a trend towards longer response time associated with unexpected, compared with expected, auditory stimuli when cues were associated with the presence or absence of sounds. Participants also showed a trend-level tendency to respond less accurately to unexpected, compared with expected, silence (where the cue had been previously associated with sound), and more accurately to unexpected, compared with expected sound (where the cue had been previously associated with silence). Response time to sounds of expected and unexpected pitch was similar, although participants were significantly more accurate in responding to unexpected low-pitched tone (when the cue had been previously associated with high-pitched tone) compared with expected low-pitched tone.

One possible explanation for non-significant results of this study could involve the strength of auditory representations. It is plausible that sounds are best learned in associations with shapes when they form part of a more complex system, e.g. language [(Aleksandrov et al., 2010)](#_ENREF_146) and hence are more meaningful and engage more neuronal resources. However, the trend towards decreased accuracy in responding to unexpected silences found in this study could reflect an effect of a representation of sound on behavioural response to silence. On the other hand, presentation of a sound when silence is expected might attract attention due to its relative salience. It is plausible that the potentially increased response latency due to unexpectedness was reduced by the startling nature of an unexpected sound. The attention-attracting effect of unexpected sound might have also underlied the trend towards improve accuracy of responses. Similarly, significantly increased accuracy associated with presentation of a low-pitched sound when a high-pitched tone was expected might have been due to an attention- and thus accuracy-enhancing effect.

Therefore, it appears that when visual cues are associated with the presence and absence of sound and with sounds of different pitch, the relationship between expectation and behavioural measures of cognitive processes might depend on the attributes of the auditory stimuli in contrast with other auditory stimuli. Such attributes might not, however, affect neural activity. Hence, the following experiments described in chapters 4,5 and 6 will investigate neural correlates of processing auditory stimuli presented outside of the learned associations. The lack of significant result in the Behavioural Sound/Silence experiment could have been to the startling, possibly attention-grabbing effect of unexpected sound, which reduced the response time. Such reduction in response time could have cancelled a potential effect of expectation on behaviour. There was, however, a trend in the predicted direction. Moreover, it is possible that the interaction between salience and expectation might not affect the neural processes in the same way as it affected the behavioural response. Since there was a trend towards prediction-dependent increase in response time, the neural underpinnings of auditory expectation were investigated using the same paradigm.

The difference in the reaction time in the Behavioural Pitch Experiment was not significant. However, there was a significant difference in accuracy. Functional MRI signal is a more sensitive measure of changes in perceptual processing than reaction time (Tomasi et al., 2004). Hence, the FMRI Pitch experiment will investigate whether processing sounds of unexpected pitch is associated with changes in neural activity.

One of the limitations of the studies described in this chapter could be an insufficient acoustic contrast between the low- and high-pitched stimuli. It is plausible that a greater difference between the pitch of the tones would evoke a difference in response time to unexpected stimuli (i.e. when a low-pitched stimulus is presented instead of a high-pitched tone and vice versa). Another limitation may be the attentional requirements of the task. It could be that the extent to which participants concentrated on the task reduced their ability to learn the associations. However, fMRI studies indicate that learning should take place even when participants pay no attention to the stimuli.

# Chapter 4

# Neural basis of auditory predictive coding

**Abstract**

Normal perception relies on predictive coding, in which neural networks establish associations among stimuli and form predictions of expected input. Stimuli that do not match the prediction evoke a signal called prediction error. We propose that auditory hallucinations are underpinned by a mechanism where processing of prediction error is impaired, leading to increased role of expectation in perceiving sounds.

In this fMRI study we investigated normal auditory predictive coding that might help explain the mechanisms of auditory hallucinations. We hypothesised that auditory cortex would show increased response to unexpected, compared with expected, auditory stimuli. Twelve healthy participants completed a task consisting of pairs of stimuli to induce learning of associations and contrast conditions of expected and unexpected sounds and silences. When cued by the visual stimulus, participants indicated whether the auditory stimulus in the current trial contained sound or silence (FMRI Sound/Silence Experiment) and low-and high-pitched sound (FMRI Pitch Experiment).

Unexpected auditory events, whether sound or silence, evoked greater activation in the left MTG than corresponding expected events. Unexpected sounds, but not unexpected silence, versus those expected, evoked greater activation in the left STG. Low, compared with high-pitched sounds were associated with greater activity in the bilateral MTG.

These findings suggest that the superior and middle temporal gyrus perform different functions in integrating sensory information with predictive signals during auditory perception. We discuss these findings in terms of a model of auditory predictive coding in normal perception, and suggest how this model may help explain the occurrence of auditory hallucinations in clinical populations.

## 4.1. Introduction

Normal perception consists of an interaction between two types of processing: top-down (expectation driven) and bottom-up (stimulus driven). The predictive coding model of perception posits that neural networks enable the learning of associations between perceived stimuli and the formation of predictions relating to incoming input (Rao and Ballard, 1999). For example, the sound of an engine triggers the prediction of an approaching vehicle. Forming predictive representations of incoming signals is likely to conserve neural resources by reducing the amount of processing required when the expected stimulus occurs (Bubic et al., 2010). However, the ability to adapt to a rapidly changing environment relies upon recognition of discrepancies between expected and actual stimulation, and the updating of future expectations accordingly (Friedman et al., 2009). For instance, detection of unexpected sounds in a car engine may help identify a mechanical problem. At a neural level these functions are most likely achieved through a hierarchical structure where each processing level in the brain transmits the expectation to the lower level via feedback pathways. The lower level then compares this expected input to the actual, external stimulation received and returns a residual error signal (prediction error) communicating any difference between the two, to the higher level via feedforward pathways.

Mismatch negativity (MMN) refers to an enhanced brain wave potential evoked by a deviant sound in a string of standard sounds, believed to represent the prediction error (Naatanen et al., 1982, Winkler, 2007). Functional MRI studies show that the network involved in the processing of a deviant sound involves superior and middle temporal gyri (auditory cortex) (Opitz et al., 2002, Kim et al., 2009, Schall et al., 2003). However, MMN is usually generated via paradigms where expectation of a stimulus is generated through repetition (i.e. the stimulus predicts itself). In contrast, ‘real world’ associations are often a consequence of more complex patterns of stimulation, where one event predicts another, different, event. Hence, a paradigm involving learning associations between two different stimuli might be more appropriate for studying predictive coding. Such a paradigm could be based on the Rescorla-Wagner model of associative learning (1972, Schultz and Dickinson, 2000) (refer to Chapter 2 Section 1). This model suggests that once the association between a cue and the cued outcome has been learnt, unexpected outcomes evoke a prediction error signal that changes the strength of the subsequent associations between the stimuli (cue and outcome) and allows the modification of the future prediction.

Previous functional MRI studies have demonstrated prediction error as increased activity in brain areas engaged in learning associations, e.g. PFC in cognitive tasks and visual cortex in audio-visual tasks (Fletcher et al., 2001, den Ouden et al., 2009, den Ouden et al., 2010). Furthermore, this increase in activity is greater for unexpected events (which follow cues that have previously been presented on their own) than for unexpected omissions (which occur when an expected event does not happen) (Fletcher et al., 2001).

We propose that learning of associations between auditory perceptions and certain activities and emotions underlies the formation of auditory hallucinations. For instance, an activity might be associated with a heard disdainful commentary. As a result, this activity could then act as a cue for the stored perception of negative commentary, possibly in combination with a low mood. The reduced auditory prediction error seen in schizophrenia (Umbricht et al., 2006) may impair the effect of the (contradictory) external input in correcting the prediction, thus allowing abnormal auditory expectation to prevail. Such misconstruing of internal sensory representation may thus lead to heard perceptions in the absence of external input. Further, impaired prediction error signals are likely to lead to insufficient updating of internal models of the external world during instances where expectation is incorrect. This impairment, in the long term, is likely to result in an increasing disparity between the internal world of the individual and the environment (as may occur in psychosis) (Fletcher and Frith, 2009).

## 4.2. FMRI Sound/Silence: silence substituted with sound

### 4.2.1. Aims

The expectation-perception hypothesis of auditory hallucinations proposes that the ‘voices’ occur when insufficient prediction error allows the prediction of sound to prevail even when no sound is occurring (an ‘unexpected omission’ in associative learning terminology) or when external input consists of another sound (‘unexpected events’). We therefore set out to investigate the process of auditory predictive coding in healthy individuals using fMRI to examine exactly how violations of expectation, including both unexpected events and omissions, are processed in the auditory and prefrontal cortex. We developed an associative learning task consisting of pairs of stimuli and contrasted conditions of expected and unexpected sounds and silences. When cued by a visual stimulus, participants indicated whether an auditory stimulus was sound or silence. Whilst the majority of the auditory stimuli were presented in the context of their previously learnt pairs (i.e. they were expected), the minority appeared in mismatched pairs (i.e. they were unexpected). Previous research has provided evidence that regions involved in learning associations between stimuli show increased activity in response to unexpected outcomes, and that this increase is greater for unexpected cue-outcome pairings (unexpected event when none was predicted) than for unexpected cue-no outcome pairings (lack of expected event) (Fletcher et al., 2001).

### 4.2.2. Hypotheses

Hence, **hypothesis 1**) predicted that once participants learned associations between the visual and auditory stimuli, auditory events that violate the learnt expectation would evoke greater activity in the auditory cortex than items that match expectation, even in situations where the auditory stimuli was in fact silence.

Specifically, **hypothesis 2)** stated that in fMRI Sound/Silence Experiment following the visual cue, unexpected silence (i.e. silence when the cue had previously been associated with sound) would induce greater activity than an expected silence in auditory cortex.

**Hypothesis 3**) predicted that unexpected sound (i.e. a sound when the cue had been associated with silence) would evoke greater activity in the auditory cortex than an expected sound.

**Hypothesis 4**) stated that an increase in activity in auditory cortex evoked by unexpected sound would be greater than an increase evoked by unexpected silence.

Another aim of this study was to examine effective connectivity, i.e. causal effects of activity in some brain areas on activity in other areas, underpinning auditory predictive coding. More precisely, we employed psychophysiological interaction analysis (PPI, Friston et al., 1997), see section 2.3) in order to identify regions that modulate activity in auditory cortex in different experimental contexts. We aimed to establish which areas would show significant increase in effective connectivity with auditory cortex in conditions of 1) unexpected, compared with expected, silence and sounds combined, 2) sound, compared with silence, 3) silence, compared with sound, 4) unexpected, compared with expected, sound and 5) unexpected, compared with expected, silence.

It has been shown that processing of prediction error is associated with enhanced effective connectivity between areas processing the cue and the outcome [(den Ouden et al., 2009)](#_ENREF_14). Since frontal areas, including the inferior and middle frontal gyrus, activate in silent expectation of sound [(Leaver et al., 2009)](#_ENREF_5) and in processing of MMN (Schall et al., 2003), they might also form part of the neural pathway processing prediction error. Therefore, **hypothesis 5**) predicted that visual cortex, prefrontal cortex and middle temporal gyrus would show increased effective connectivity with auditory cortex in the condition of unexpected, compared with expected, sounds and silence.

Since insula has been shown to be involved in auditory perception (Bamiou et al., 2003), **hypothesis 6)** stated that auditory cortex would show greater effective connectivity within itself, as well as with auditory insula in response to sound, than in response to silence.

**Hypothesis 7**) predicted that unexpected sounds would evoke greater connectivity of auditory cortex with prefrontal and visual cortices, as well as insula, than expected sound.

Finally, activity in auditory cortex in silence appears to be modulated by ACC [(Hunter et al., 2006)](#_ENREF_71). Hence, h**ypothesis 8**) stated that in the condition of silence, compared with sound, auditory cortex would show increased effective connectivity with ACC.

**Hypothesis 9**) predicted that areas involved in responding to unexpected auditory stimuli and to silence (prefrontal and visual cortices as well as ACC) would modulate auditory cortex in the condition of unexpected, compared with expected, silence.

### 4.2.3. Method

For information on participants, questionnaires, general procedure, scanning and data preprocessing – refer to Chapter 2, Section 2.4.1, 2.4.2, 2.4.3., 2.4.4 and 2.4.5.

#### 4.2.3.1. Stimuli

Stimuli were presented using commercially available ‘Presentation’ software (Neurobehavioral Systems, Albany, USA, www.neurobs.com). In the acquisition stage, visual stimuli were presented on a computer screen and auditory stimuli were delivered over the headphones. In the scanner visual stimuli were presented to the participant via a projector-screen system with a mirror fitted over the radiofrequency head coil and auditory stimuli were delivered via a MRI compatible sound system over headphones. Visual stimuli consisted of a vertical rectangle and a horizontal rectangle, unfilled, white and presented on the black background. Words ‘silence/sound’ were printed in white overlaid on a black background. A 440 Hz tone of 500 ms duration, created in open source software (Audacity: [www.audacity.sourceforge.net](http://www.audacity.sourceforge.net)) was used as the auditory stimulus. As a baseline, a static white fixation cross was presented in the centre of the black background.

#### 4.2.3.2. Procedure

For information on the general procedure refer to Chapter 2 section 2.4.3.

The experiment consisted of two phases: an acquisition phase, in which participants learned associations, and a scanning phase, in which expected auditory stimuli where contrasted with unexpected ones. Fifteen to twenty trials conforming to the contingency is sufficient to induce learning of complex rules (Bendixen et al., 2008). Since sparse-sampling method of neuroimaging requires prolonged time between consecutive trials (12.5 s), the current study employed smaller number of trials compared with the Behavioural Sound/Silence and Pitch experiments. Increased neural activity in response to unexpected outcome has been found in studies employing 12 -30 expected and 6-18 unexpected trials for each pair of stimuli (Corlett et al., 2004, 2007, Menon et al., 2007). The current study employed 48 trials, including 36 expected and 12 unexpected trials.

**Acquisition phase**

In the acquisition phase participants implicitly learned associations between shapes and sounds in a quiet room. Participants were firstly presented with one of the shapes (vertical or horizontal rectangle) and after a 500ms gap, with both shapes side-by side. They were required to respond as to whether the initially presented shape appeared on the left or the right. Following a further 500ms pause the words ‘sound’ and ‘silence’ appeared on the screen accompanied by either the presence or absence of an auditory stimulus (a sinusoidal tone). Participants were required to indicate whether the text describing the actual auditory stimulation appeared on the left or the right. Unbeknownst to the participants, a vertical rectangle was always followed by a tone (30 trials) whereas a horizontal rectangle was always followed by silence (30 trials). Trials were separated by 1 s and their order was randomized. Responses ensured that participants paid attention to the stimuli. This stage took approximately 5 minutes.

**Mismatch phase**

The mismatch phase was completed whilst the participant was in the scanner and took the form of a mixed design. The refresher session before scanning commenced presented participants with 20 repetitions of the associations from the acquisition stage: a vertical rectangle-tone (10 trials) and a horizontal rectangle-silence (10 trials), in randomized order. The refresher was followed by 3 blocks of mismatch trials, 16 trials in each block (48 trials altogether), in which expected sounds and silence were contrasted with unexpected sounds and silence. In 25% of trials the visual cues were followed by unexpected outcome, i.e. the vertical rectangle was followed by silence and the horizontal rectangle was followed by sound. Each block of 16 trials consisted of the following pairings: 6 repetitions of the vertical rectangle-tone (expected sound), 6 repetitions of the horizontal-rectangle-silence (expected silence), 2 repetitions of the vertical rectangle-silence (unexpected silence) and 2 repetitions of the horizontal rectangle-sound (unexpected sound). The order of the trials was pseudo-randomized so that the unexpected auditory stimuli did not appear in the first 4 trials. The pause between presentation of the pair of shapes and an auditory stimulus was set at 750 ms (using average reaction time from the Behavioural Sound/Silence Experiment as guidelines). Unlike in the acquisition phase, participants were not required to respond to the sounds. The experimental blocks were separated by two blocks of 8 baseline trials each (16 trials altogether), during which participants were presented with a fixation cross and asked to respond to it by pressing the second button on the response box with their index finger, to control for the motor action in response to the shape in the experimental trials. The fixation cross appeared at the same time point as the pair of shapes in the experimental blocks. In addition to experimental and baseline trials, the first time-point of each block presented participants with instructions as to the task they should perform during that block. This part of experiment took 14 min 45s.

#### 4.2.3.3. Data analysis

**Behavioural analysis**

Response time to shapes was recorded in tens of milliseconds, converted to milliseconds and analyzed with a repeated-measures t-test.

sound silence



500 ms

500 ms

Until response detected

Until response detected

Until response detected

500 ms

500 ms

Until response detected

500 ms



500 ms

sound silence

Tone

Silence

**Figure 4.1. Task design in the acquisition phase**. Participants responded to both visual and auditory stimuli. The vertical and horizontal rectangles appeared simultaneously and remained on the screen until a response was detected. Participants pressed the right arrow key if the shape on the right from the centre of the screen corresponded to the previously presented single shape and the left arrow key if the shape on the left from the centre of the screen corresponded to the previously presented single shape. In the mismatch phase participants pressed the second button on the response box with their index finger if the target shape was on the left from the centre of the screen, and the third button on the response box with their middle finger if the target shape was on the right from the centre of the screen. Response to the sound (required in the acquisition phase only) was cued by words ‘sound’ and ‘silence’ appearing in the centre of the screen simultaneously with auditory events until response was recorded. Participants pressed the right arrow key when the word on the right from the centre of the screen corresponded to what they heard and the left arrow key if the word on the left from the centre of the screen corresponded to what they heard. Position of the shapes and words on the screen was randomized.

**FMRI analysis**

Data from the mismatch phase of the FMRI Sound/Silence Experiment were analysed with a voxel-wise general linear model (GLM). First, contrasts were estimated at a single-participant level. These estimates were then entered into a second level, random effect model. We assumed non-independence of images from the same participant and unequal variance between conditions and participants. In the group level analysis participant and condition were modelled as predictors using a flexible factorial design. We identified voxels which responded to all experimental stimuli (expected and unexpected sounds and silence) versus a fixation cross baseline at p<0.01, uncorrected. These voxels formed the volume-of-interest (VOI).

The creation of the VOI aimed to decrease the risk of type I error by decreasing the number of comparisons performed. Next, we performed t-tests to compare unexpected stimuli (sounds and silence) with expected stimuli (sounds and silence). This was followed by comparison, using t-tests, of unexpected and expected sounds and silences combined, unexpected and expected sounds only and unexpected and expected silence only. Each of the contrast was performed within the whole brain and within the VOI. The statistical threshold for reporting was p<0.05, family-wise-error (FWE) corrected at voxel level. MNI coordinates were converted to Talairach and Tournoux space using the mni2tal software routine in Matlab. Anatomical locations were identified using the Talairach and Tournoux paper atlas [(1988)](#_ENREF_159).

**Connectivity fMRI analysis**

Psychophysiological interactions is an optimal approach in investigating connectivity if only one ROI is available and the aim of the analysis is to search for areas that are connected with it (Hunter et al., 2010, Kilian-Hutten et al., 2011). Therefore, PPI was applied in the current study. First step of the effective connectivity analysis involved identifying regions that show increased effective connectivity with the auditory cortex in the condition of 1) all unexpected, versus all expected, stimuli, 2) sounds versus silence and 3) silence versus sound. We identified the voxel of maximum activation in the group contrast of all experimental stimuli versus fixation cross baseline at p>0.001, uncorrected. This voxel was identified as group seed region. We then searched individual participants’ contrasts images of all experimental stimuli versus fixation cross displayed at p<0.05, uncorrected, for a voxel with the highest *t* statistics in the brain area where the group seed was identified. This voxel was the participant-specific seed region. The first eignevariate of the time-course data was extracted from a 5-mm sphere with seed regions as the centre for each participant. The mean value of the eignevariate was then subtracted from each time point value, creating a time course vector with 69 time points (the physiological variable).

Parametric connectivity contrast images were produced in the first-level analysis for every participant with the goal of identifying areas that show increased connectivity with the seed area in the condition of unexpected, versus expected, stimuli. First, the time-course vector was multiplied with the vector representing the condition (the psychological variable). The condition vector was represented by values: unexpected stimulus (+1), expected stimulus (-1), fixation cross (0), instructions (0). The multiplication generated the psychophysiological interaction (PPI) term. The PPI term was then entered into the first-level analysis as an effect of interest. The time course and the condition were entered as effects of no interest. The first-level analysis generated parametric connectivity contrast images for each participant’s scans. These contrast images were then entered into a group-level analysis in a flexible factorial model with participant and condition as factors.

Parametric connectivity contrast images were also produced for each participant in order to identify areas that show increased connectivity with the seed area in the condition of sound, versus silence and silence, versus sound. In the first-level analysis the psychophysiological interaction term (PPI) was produced by multiplying the time-course vector with the condition vector: sound stimulus (+1), silence stimulus (-1), fixation cross (0), instructions (0). The PPI term was entered as an effect of interest, whilst the time course and the condition were entered as effects of no interest. The first-level analysis generated parametric connectivity contrast images for each participant’s scans. These contrast images were then entered into a group-level analysis in a flexible factorial model with participant and condition as factors.

Finally, the above procedure was repeated in order to generate parametric connectivity contrast images in the condition of unexpected, compared with expected, sound. The seed region was the voxel of maximum activation in the group contrast of all sound stimuli (expected and unexpected) versus fixation cross at p<0.001, uncorrected. We then searched individual participants’ contrasts images of all sound stimuli versus fixation cross displayed at p<0.05, uncorrected, for a voxel with the highest *t* statistics in the area of the group seed. This voxel was the participant-specific seed region. The auditory condition was described as follows: unexpected sound stimulus (+1), expected sound stimulus (-1), fixation cross (0) and instructions (0). The low level of activation evoked by silence meant that it was not possible to find participant-specific seed regions. Hence, we did not search for areas that would show increased connectivity in the condition of unexpected, compared with expected, silence.

The statistical threshold for significance was p<0.05, FWE- corrected at voxel level. A t-test was performed to identify areas that show significantly increased activity in the condition of unexpected, compared with expected, silence and sounds. The inverse contrast was not practical due to the difference in power (the number of expected stimuli was three times higher than the number of unexpected stimuli). We also employed t-tests to identify areas that showed significantly increased connectivity with the seed area in the condition of sound relative to silence, as well as areas that show significantly increased connectivity with auditory cortex in the condition of silence relative to sound. Then we performed a t-test to search for regions that exhibited enhanced connectivity with the seed region in the condition of unexpected, compared with expected, sound.

### 4.2.4. Results

#### 4.2.4.1. Behavioural results

A related samples t-test revealed that response time to the vertical rectangle (mean 448.46 ms, SD=54.72) was not significantly different to response time to the horizontal rectangle (mean =443.16, SD=62.77, t(11)=0.36, p=0.72). A Wilcoxon signed-rank test revealed no significant difference between accuracy in responding to the vertical and horizontal rectangle (T=4, p=0.7). Accuracy of responses to shapes was above 90%.

#### 4.2.4.2. FMRI results

Brain areas activated by all experimental stimuli (expected sounds, unexpected sounds, expected silences and unexpected silences) versus observance of a fixation cross (baseline) at p<0.01, uncorrected, are shown in Table 4.1. These areas, which included bilateral auditory cortex, served as the volume-of-interest (VOI) for the subsequent family-wise error (FWE)-corrected statistical comparisons.

Whole brain analysis

The contrast of all unexpected stimuli (sounds and silences together) versus all expected stimuli revealed no significant activations in the whole brain analysis. The contrast of unexpected versus expected sounds showed that left insula responded to unexpected sound significantly more than to expected sound in the whole brain analysis (Table 4.2). The contrast of unexpected versus expected silence revealed no significant activations in the whole brain analysis.

VOI analysis

The contrast of all unexpected stimuli (sounds and silences together) versus all expected stimuli revealed significant activation in the left MTG and in the left STG within the VOI (Table 4.2, Figure 4.2a). The contrast of unexpected and expected sounds showed that within the VOI left STG responded to unexpected sound significantly more than to expected sound (Table 4.2, Figure 4.2b, c). Given that different activation areas were found between unexpected sounds and unexpected sounds and silences combined, we examined parameter estimates for these activations (Table 4.2) in each of the four conditions (expected silence, unexpected silence, expected sound, unexpected sound) compared with baseline. This analysis revealed that left MTG responded with increased activation to unexpected, compared with expected, sounds and silence (Figure 4.3a) whilst left STG responded with increased activation to unexpected, compared with expected sounds (Figure 4.3b).

#### 4.2.4.3. Effective connectivity results.

The first step of the effective connectivity analysis involved identifying the seed area in the condition of all unexpected, versus all expected, stimuli, as well as sound versus silence and silence versus sound. The seed area in this condition was in the left superior temporal sulcus (t=5.93, p<0.008, FWE-corrected in the whole brain, MNI coordinates: -52 -10 -6). The participant-specific seed area therefore was the voxel with the highest *t*-statistic in the area of the left superior and middle temporal **Table 4.1. Brain areas activated by experimental stimuli compared with fixation cross baseline.**

|  |  |  |  |
| --- | --- | --- | --- |
| Region | Peak t | MNI coordinates | Cluster size |
| Left hemisphere |  |  |  |
| Superior temporal sulcus | 5.93 | -52 -10 -6 | 1575 |
| Central sulcus | 4.46 | -28 -20 38 | 113 |
| Lingual gyrus | 3.08 | -8 -70 -6 | 78 |
| Caudate nucleus | 2.83 | -4 18 10 | 36 |
| Precentral gyrus | 2.56 | -38 -26 62 | 12 |
| Right hemisphere |  |  |  |
| Superior temporal gyrus | 5.32 | 42 -26 6 | 2304 |
|  | 2.58 | 54 0 0 | 9 |
| Precuneus | 4.24 | 8 -70 20 | 1396 |
| Caudate nucleus | 3.42 | 24 -20 22 | 326 |
| Inferior parietal lobule | 3.61 | 30 -58 38 | 311 |
| Cingulate gyrus | 3.98 | 10 26 8 | 138 |
| Postcentral sulcus | 3.98 | 42 -26 38 | 60 |
| Superior parietal lobule | 3.59 | 22 -58 64 | 23 |
| Middle frontal gyrus | 3.24 | 38 50 -6 | 32 |
|  | 2.80 | 30 -8 40 | 10 |
| Inferior frontal gyrus | 2.90 | 46 44 12 | 11 |
| Middle temporal gyrus | 2.79 | 56 -60 4 | 19 |
|  | 2.55 | 44 -56 6 | 6 |

Areas where activation was significant in response to all experimental stimuli (expected and unexpected sounds and silence), compared with fixation cross, at p<0.001 uncorrected. Peak t = test statistic at the voxel showing greatest activity in a cluster. Cluster – number of voxels in a cluster at p<0.01, uncorrected. MNI- Montreal Neurological Institute.

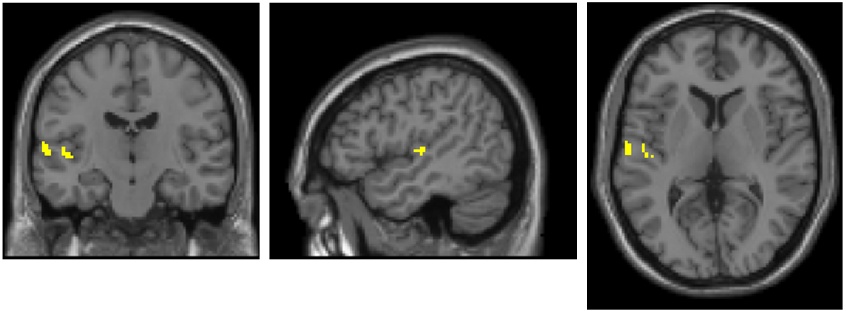
**Table 4.2. Areas that produced significantly greater response to unexpected than expected silence and sounds.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Region (Brodmann area) | Peak *t* | FWE *p* | MNI coordinates (*x y z*) | Cluster |
| L MTG (22/21)a | 5.27 | 0.001 | -42 -18 -10 | 312 |
| L STG (22)a | 4.04 | 0.025 | -44 -30 2 | 27 |
| L insulab | 6.78 | 0.000 | -34 -12 6 | 2511 |
| L STG (21)c | 4.16 | 0.018 | -48 -16 6 | 30 |
| L STG (22)c | 3.97 | 0.031 | -62 -10 8 | 55 |

Brain areas where activation increased significantly in response to unexpected, compared with expected, sounds and silence at p<0.05 corrected for family-wise error (FWE). Peak *t*- test statistic at the voxel showing greatest activity in a cluster. Cluster – number of voxels in a cluster at p<0.001, uncorrected. MNI- Montreal Neurological Institute. L- left, R- right. MTG – middle temporal gyrus. STG- superior temporal gyrus.

1. Brain areas activated significantly more by unexpected, compared with expected, sounds and silence together within the volume of interest (VOI)
2. Brain area activated significantly more by unexpected, compared with expected, sounds in the whole brain
3. Brain areas activated significantly more by unexpected, compared with expected, sounds within the volume of interest (VOI)

gyrus. No areas showed significantly increased effective connectivity with the seed area in the contrast of unexpected (sounds and silences) versus expected stimuli either in the whole brain or within the VOI. Comparison of sounds with silence revealed no significant activations in the whole brain or within the VOI. No areas showed increased effective connectivity with the seed areas in the contrast of silence versus sound in the whole brain or within the VOI.

E:\phd\theses\drafts\sound-silence as paper\image\image main effect mask MTG focus.TIFG:\phd\theses\drafts\sound-silence as paper\image\image interaction whole brain (insula).TIF

**c**

**b**

**a**

**Figure 4.2. Areas that showed signficant activations in contrasts of unexpected, versus expected, auditory stimuli.** Activations (listed in Table 4.2) are mapped on the coronal, saggital and axial surface (from left to right) of a single- subject canonical brain. Voxel threshold was p<0.05 FWE-corrected. a) Unexpected sounds and silence, combined, evoked significantly greater activation than expected sounds and silence (yellow) in the left middle and superior temporal gyri within the VOI. The saggital view shows both foci of activations, while the coronal and axial views reveal the main focus in the left MTG. b) Unexpected sounds evoked significantly greater activation than expected sounds (blue) in the left insula in the whole brain analysis. c) Unexpected sounds evoked signficantly greater activation than expected sounds (yellow) in the left STG within the VOI. The two foci of activation overlap on the saggital view.



**a**



**b**

**Figure 4.3. Contrast parameter estimates in auditory cortex.** Parameter estimates in each of the four (conditions of expected silence, unexpected silence, expected sound, unexpected sound) compared with fixation cross baseline in a) left MTG and b) left STG. Error bars are at 90% confidence intervals.

The seed area for the analysis of connectivity in the condition of unexpected versus expected sound was in the right STG (t=8.53, p<0.001 FWE-corrected, 2833 voxels, MNI coordinates: 42 -26 6). Individual-level seed area was the cluster with the highest *t*-statistic in the right superior or middle temporal gyrus. No areas showed significantly increased connectivity with the seed area in the contrast of unexpected, compared with expected, sound either in the whole brain or within the VOI.

### 

### 4.2.5. Discussion

The predictive coding model of perception proposes that each processing level in the brain forms predictions of an incoming stimulus and transmits these predictions to the lower processing level (Rao and Ballard, 1999). The lower level in turn compares the received information with actual external stimuli. If the external stimulus does not match the expectation, a prediction error signal is generated and sent to the higher level. Prediction error signal is reflected in increased activity that is specific to the modality of the unexpected stimulus (den Ouden et al., 2010, den Ouden et al., 2009). Using an associative learning task, we found an enhanced response to auditory stimuli, that did not match expectation, in the left superior and middle temporal gyri. This finding is in agreement with the hypothesis, which stated that auditory cortex would respond with significantly increased activity to unexpected, compared with expected, auditory stimuli. This result is also in line with previous studies using an oddball paradigm (where a string of identical sounds was contrasted with an occasional different sound) (Kim et al., 2009, Opitz et al., 2002, Schall et al., 2003). Therefore, our results support the theory that the left superior and temporal gyri generate auditory prediction error.

However, our findings also revealed that a potential specialization within the temporal cortex in the processing of auditory prediction error (Figure 4.4). Specifically, while MTG engaged during processing of both unexpected sound (when silence is predicted) and unexpected silence (when sound is predicted), STG only responded to a significant extent to unexpected sound. Such difference in the pattern of activation suggests that whilst activity in MTG is modulated by expectation regardless of the external input, activity in STG is regulated by prediction mainly when the incoming stimulus is sound. Hence, the middle and superior temporal gyri might form a hierarchy in predictive coding such that MTG relays the auditory expectation to STG. Such hierarchy has been noted in both anatomical and functional aspects of perception (Friston, 2003). Superior temporal gyrus appears to be specialized in responding and analyzing sounds rather than silences. If MTG constitutes a higher level in hierarchy, it might be responsible for more abstract analysis and interpretation of auditory input, including assigning meaning to the activity (or lack of activity) at the lower level (STG). Even if the expected stimulus is silence, its prediction in the left MTG is associated increased activity in relation to baseline. Such increase in expectation of no stimulus might be related to a potential need to inhibit a response, as well as to directing attention to the state of the external environment. In STG the transmitted expectation would evoke a pattern of activation more specific to the external stimuli. Thus, expected and unexpected silence would be associated with a low level of activity, whilst unexpected sound would activate a relatively large group of neurons. Interpretation of this pattern of STG activity performed by MTG appears to result in a response format that is loosely related to the type (or presence) of a stimulus. Such a mechanism could potentially explain why the MTG response to unexpected sound is similar to STG response to the same stimulus, whilst its response to unexpected silence is greater than that of the STG (but smaller than the MTG’s own response to sound). Indeed the middle temporal gyrus is a central component of auditory processing of complex auditory stimuli such as speech (Davis and Johnsrude, 2003) and is involved in extracting meaning from ambiguous auditory stimuli (Kilian-Hutten et al., 2011).

A plausible mechanism underpinning the enhanced activity in response to stimuli that do not match the prediction could involve an interaction between visual and auditory cortices. More specifically, once associations between the stimuli are learned, processing of the visual cue might induce retrieval of a predictive representation of the auditory stimulus in the auditory cortex. If the visual cue induced a retrieval of a predictive representation of silence, MTG would form an expectation of silence and convey it to STG (E0, Figure 4.4a). Setting up an expectation is thought to stimulate an increase in neural firing in the target area (in this case in MTG followed by STG) and to induce the synchronization of the firing between the regions involved (Lauwereyns et al., 2002, Watanabe and Hikosaka, 2005). Synchronized firing allows the neural populations to coordinate their phases of greatest excitability and thus process the stimulus more efficiently. If the external input matches the prediction, a relatively low level of the stimulus-evoked activity is required for the signal to be processed as this signal is summated with the activity representing expectation (Becker et al., 2011). However, if the input coming from the ear was sound (S1, Figure 4.4a), STG would compare it with the expectation received from MTG and would send the prediction error (PE1=S1-E0, Figure 4.4a). Conversely, in instances where sound is expected, MTG would send an expectation of the input to STG (E1, Figure 4.4b). If no external stimulus is encountered (unexpected silence), STG would respond with only minor increase in activity (S0, Figure 4.4b). Middle temporal gyrus would then compare the prediction with little or no activity in STG and generate a prediction error signal (PE0=S0-E1, Figure 4.4b). It has been suggested that enhanced activity associated with prediction error, compared with processing expected stimuli is underpinned by the formation of a new neural pathway, needed to transmit the unexpected information (Strelnikov, 2007).

No areas showed increased effective connectivity with auditory cortex in any of the conditions. This is not in line with the hypotheses, which predicted that activity in the auditory cortex would be modulated by PFC and visual cortex (in the condition of unexpected, versus expected, stimuli), by the insula (sound compared with silence) and by ACC (silence compared with sound). Such lack of significant activations in the connectivity analysis could be due to insufficient power. Half of the experimental trials contained no auditory stimulus (silence) and were therefore associated with lower, relative to sound trials, level of activity in the auditory cortex.

Finally, we did not predict the increased activation of the insula during unexpected, versus expected, sound stimulation. However, this area is involved in the directing auditory attention and the processing of novel sounds (Bamiou et al., 2003).

**c**

**b**

**S1**

**E0**

PE1=S1-E0

**MTG**

**STG**

PE1=S1-E0

**PE1**

**a**

**S0**

**E1**

PE0=S0-E1

S0

**MTG**

**STG**

**S0**

**S1**

**E1**

PE1=S1-E1

**MTG**

**STG**

PE1=S1-E1

**PE1**

**S0**

**E0**

PE0=S0-E0

**STG**

S0

**PE0**

**MTG**

**d**

**Figure 4.4. Model of normal auditory predictive coding.** a). Prediction: silence, external input: sound b) Prediction: sound, external stimulus: silence. c) Prediction: sound, external input: matching sound. d) Prediction: silence, external input: silence. PE in 4.4d < PE in 4.4c< PE in 4.4b< PE in 4.4a.

STG – superior temporal gyrus, MTG – middle temporal gyrus, S0- silent input, E1 – expectation of sound, PE0 – prediction error signalling silence, S1- sound input, E0 – expectation of silence, PE1 – prediction error signalling sound.

Voisin and colleagues (2006) found that STG activity increased during the anticipation of sound, which did not occur (i.e. unexpected silence). It should be noted, however, that in their study the other condition was a resting state scan (no expectation). Hence the increased response of STG found was most likely due to increased attention towards the auditory modality, as activity in STG increases with attention (Woodruff et al., 1996). The current study controls for attention by varying the accuracy rather than the presence of expectation, independent of the task the participants were performing. Therefore the differences in activation found in the current study are unlikely to be due to differences in attention that are unrelated to those induced by expectation.

## 4.3. FMRI Pitch Experiment: sound substituted with another sound.

### 4.3.1. Aims

It could be that auditory hallucinations occur when reduced generation and processing of prediction error allows the prediction of sound to prevail even when a different sound is occurring (‘unexpected events’). Hence, the current study investigated the process of auditory predictive coding in healthy individuals using fMRI to examine exactly how violations of expectation of sound are processed in the auditory cortex. To accomplish this, we developed an associative learning task, consisting of pairs of stimuli and contrasted conditions of expected and unexpected low- and high-pitched sounds. Evidence suggests that regions involved in processing the outcomes (in this case – the tones) show increased activity in response to a breach of expectation (Opitz et al., 2005, den Ouden et al., 2009).

### 4.3.2. Hypotheses

It was predicted that the sounds of unexpected pitch would evoke greater activity in the auditory cortex than sounds of expected pitch (**hypothesis 1**).

**Hypothesis 2)** predicted that an unexpected low pitched-sound (i.e. when the cue had previously been associated with a high-pitched sound) would evoke enhanced response in auditory cortex, compared with an expected low-pitched sound.

Unexpected high-pitched sound (i.e. a high-pitched sound when the cue had previously been associated with a low-pitched sound) would induce greater activity in auditory cortex than expected high-pitched sound (**hypothesis 3**).

There would be no difference between activity in auditory cortex in response to low- and high-pitched tones (**hypothesis 4**).

We also investigated effective connectivity of auditory cortex, i.e. causal influence of activity in some brain areas on activity in auditory cortex. Psychophysiological interaction analysis (PPI, Friston et al., 1997, see Section 2.3) was employed in order to elucidate which areas of the brain modulated activity in the auditory cortex in the condition of 1) sounds of unexpected, compared with expected, pitch, 2) low-, compared with high-pitched sounds, 3) high-, compared with low-pitched sounds, 4) unexpected, compared with expected, low-pitched sounds and 5) unexpected, compared with expected, high-pitched sounds.

Evidence suggests that prediction error is underpinned by increased effective connectivity between areas processing the cue and the outcome [(den Ouden et al., 2009)](#_ENREF_14). Expectation and its modification as a result of a prediction error is likely to be generated in the frontal areas [(Leaver et al., 2009](#_ENREF_5), Schall et al., 2003). Hence, we predicted that visual and prefrontal cortices would show increased connectivity with auditory cortex in response to sounds of unexpected, compared with expected, pitch (**hypothesis 5**).

There would be no difference in effective connectivity of auditory cortex in processing of low- and high-pitched sounds (**hypothesis 6**).

Visual cortex and PFC would show increased connectivity with auditory cortex in response to unexpected, compared with expected, low-pitched sounds **(hypothesis 7**) and unexpected, compared with expected, high-pitched sounds (**hypothesis 8**).

### 4.3.3. Method

For information on participants, questionnaires, general procedure, scanning and data preprocessing refer to Chapter 2 section 2.4.1, 2.4.2, 2.4.3., 2.4.4 and 2.4.5.

#### 4.3.3.1. Stimuli

Stimuli were presented using commercially available ‘Presentation’ software (Neurobehavioral Systems, Albany, USA, www.neurobs.com). In the acquisition stage, visual stimuli were presented on a computer screen and auditory stimuli were delivered over the headphones. In the scanner the visual stimuli were presented via a projector-screen system with a mirror fitted over the radiofrequency head coil and auditory stimuli were delivered via a MRI compatible sound system over headphones. The visual stimuli consisted of an upward pointing triangle and a downward pointing triangle, unfilled, white and presented on the black background. Words ‘high/low’ were printed in white overlaid on a black background. A 110 and 880 Hz tones of 500 ms duration, created in open source software (Audacity: [www.audacity.sourceforge.net](http://www.audacity.sourceforge.net)) were used as auditory stimuli. As a baseline, a static white fixation cross was presented in the centre of the black background.

#### 4.3.3.2. Procedure

For information on the general procedure refer to Chapter 2 section 2.4.3.

The experiment consisted of two phases: a contingency acquisition phase, in which participants learned associations, and a mismatch phase, in which expected auditory stimuli where contrasted with unexpected ones.

**Acquisition phase**

In the acquisition phase the upward-pointing triangle was always followed by a high-pitched tone (30 trials) and the downward-pointing triangle was followed by a low-pitched tone (30 trials) (see Figure 4.5). The order of the trials was randomized. A single shape, either the upward- or downward pointing triangle, appeared in the centre of the screen for 500 ms. After another 500 ms of blank screen both shapes appeared side-by-side and remained on the screen until participant responded to it. The response was followed by 500 ms of blank screen. Finally, a high- or low-pitched tone was presented for 500 ms. Simultaneously with auditory events, words ‘high’ and ‘low’ were presented and remained on the screen until a response was recorded. Trials were separated by 1 second. This stage took approximately 5 minutes, depending on the speed of participants’ response.

**Mismatch phase**

The mismatch phase took form of a mixed design and was completed whilst the participant was in the scanner. The refresher session before scanning commenced presented participants with 10 repetitions of associations: the upoward-pointing triangle followed by the high-pitched sound and the downward-pointing triangle followed by the low-pitched sound, in randomized order. The refresher trials were followed by 3 blocks of 16 experimental trials (48 trials). In 25% of trials cues were followed by unexpected outcome, i.e. an upward-pointing triangle was followed by a low-pitched tone and a downward-pointing triangle was followed by a high-pitched tone. Each block of 16 experimental trials contained following pairs of stimuli: 6 repetitions of the downward pointing triangle - low-pitched sound (expected low-pitched sounds), 6 repetitions of the upward pointing triangle – high-pitched sound (expected high-pitched sounds), 2 repetitions of the downward pointing triangle – high-pitched sounds (unexpected high-pitched sounds) and 2 repetitions of the upward pointing triangle- low-pitched sound (unexpected low-pitched sounds). The order of the trials was pseudo-randomized so that the unexpected auditory stimuli did not appear in the first 4 trials. The pause between the presentation of the pair of shapes and an auditory stimulus was set at 750 ms (using average reaction time from the Behavioural Pitch Study as guidelines). Unlike in the acquisition phase, participants were not required to respond to the sounds. The 3 blocks of experimental trials were separated by 2 blocks of 8 baseline trials (16 trials altogether), during which participants were presented with a fixation cross and responded to it by pressing the second button on the response box with their index finger, to control for the motor action in response to the shape in the experimental trials. The fixation cross appeared at the same time point as the pair of shapes in the experimental blocks. In addition to experimental and baseline trials, the first time-point of each block presented participants with instructions as to the task they should perform during that block. This part of experiment took 14 min 45s.

#### 4.3.3.3. Data analysis

**Behavioural data analysis**

Response time to shapes was recorded in tens of milliseconds, converted to milliseconds and analyzed with a repeated measures t-test.

Low-pitched tone

High-pitched tone

low high



500 ms

500 ms

Until response detected

Until response detected

Until response detected

500 ms

500 ms

Until response detected

500 ms



500 ms

low high

**Figure 4.5. Task design in the acquisition phase (FMRI Pitch Experiment), designed to induce learning of the associations.** Participants responded to both visual and auditory stimuli. The pair of shapes appeared simultaneously in the centre of the screen and remained until a response was detected. Participants pressed the right arrow key if the shape on the right from the centre of the screen corresponded to the previously presented single shape and the left arrow key if the shape on the left from the centre of the screen corresponded to the previously presented single shape. In the mismatch phase designed to contrast expected with unexpected outcomes in the scanner participants pressed the second button on the response box with their index finger if the target shape was on the left from the centre of the screen, and the third button on the response box with their middle finger if the target shape was on the right from the centre of the screen. Response to the sound in the acquisition phase was cued by words ‘low and ‘high’ appearing in the centre of the screen simultaneously with auditory events until response was recorded. Participants pressed the right arrow key when the word on the right from the centre of the screen corresponded to what they heard and the left arrow key if the word on the left from the centre of the screen corresponded to what they heard. Position of the shapes and words on the screen was randomized.

**FMRI analysis**

Data were analysed with a voxel-wise GLM. First, contrasts were estimated at a single-participant level. These estimates were then entered into a second level, random effect model. Non-independence of images from the same participant and unequal variance between conditions and participants were assumed. In order to generate volume-of-interest (VOI) we identified voxels which responded to all stimuli (all expected and unexpected high-and low-pitched sounds) versus fixation cross baseline at p<0.01, uncorrected. We used a t-test to localize the maximum response to all unexpected (high-and low-pitched) versus all expected (high-and low-pitched) sounds. Following this we performed t-tests to search for voxels that responded to unexpected low-pitched sounds more than to expected low-pitched sounds and voxels that respond more to unexpected high-pitched sounds more than to expected high-pitched sounds. We also employed t-tests to investigate whether any areas responded significantly more to low-pitched sounds than to high-pitched sounds and to high-pitched sounds more than to low-pitched sounds. Each of these contrasts was performed within the whole brain analysis and within the VOI. The statistical threshold for reporting was p<0.05, family-wise-error (FWE) corrected at voxel level. The MNI coordinates were converted to Talairach and Tournoux space using the mni2tal software routine in Matlab. Anatomical locations were identified using the Talairach and Tournoux paper atlas [(1988)](#_ENREF_159).

**Effective connectivity fMRI analysis**

The first step of this analysis aimed to identify areas that modulate activity in auditory cortex in conditions of all unexpected, versus expected, stimuli, as well as low- compared to high-pitched sounds and in the condition of high-, compared with low-pitched sounds. The seed region for this analysis was the voxel of maximum activation in the group contrast of all experimental stimuli versus fixation cross baseline at p=.001, uncorrected. We then searched individual participants’ contrasts images of all experimental stimuli versus fixation cross displayed at p<0.05, uncorrected, for a voxel with highest *t* statistics in the area of the group seed. This voxel was the participant-specific seed region. The first eignevariate of the time-course data was extracted from the 5-mm sphere with the seed regions as the centre for each participant. The mean value of the eignevariate was then subtracted from each time point value, creating a time course vector with 69 time points (the physiological variable).

Parametric connectivity contrast images were produced in the first-level analysis for every participant with the goal of identifying areas that show increased connectivity with the seed area in the condition of all unexpected, versus all expected, stimuli. First, the time-course vector (the physiological variable) was multiplied with the vector representing the condition (the psychological variable). The condition vector was represented by values: unexpected stimuli (+1), expected stimuli (-1), fixation cross (0), instructions (0). The multiplication generated the physiological interaction term (PPI, Friston et al., 1997). The PPI term was then entered into the first-level analysis as an effect of interest. The time course and the condition were entered as effects of no interest. The first-level analysis generated parametric connectivity contrast images for each participant’s scans. These contrast images were then entered into a group-level analysis in a flexible factorial model with participant and condition as factors.

Parametric connectivity contrast images were also produced for each participant in order to identify areas that show increased connectivity with the seed area in the condition of low-, compared with high-pitched sounds and in the condition of high, compared with low-pitched sounds. In the first-level analysis the psychophysiological interaction term (PPI) was produced by multiplying the time-course vector with the condition vector: high-pitched sound (+1), low-pitched sound (-1), fixation (0), instructions (0). The PPI term was entered as an effect of interest and the time course and the paradigm were entered as effects of no interest. The first-level analysis generated parametric connectivity contrast images for each participant’s scans. These contrast images were then entered into a group-level analysis in a flexible factorial model with participant and condition as factors.

The above procedure was repeated in order to generate parametric connectivity contrast images in the condition of unexpected, compared with expected, low-pitched sound. The voxel of maximum activation in the group contrast of all low-pitched stimuli (expected and unexpected) versus fixation cross at p=0.001, uncorrected, was identified as a seed region. We then searched individual participants’ contrasts images of all low-pitched stimuli versus fixation cross displayed at p<0.05, uncorrected, for a voxel with highest t statistics in the area of the group seed. This voxel was the participant-specific seed region. The auditory condition was described as follows: unexpected low-pitched sound (+1), expected low-pitched sound (-1), fixation cross (0) and instructions (0).

In order to analyze effective connectivity in the condition of unexpected, compared with expected, high-pitched sound, the seed region was identified as the voxel cluster with maximum activation in the group contrast of all high-pitched stimuli (expected and unexpected) versus fixation cross at p=0.001, uncorrected. Individual participants’ seed area was then identified as the cluster with highest t-statistic in the area of the group seed region in individual contrasts of all high-pitched stimuli versus fixation cross at p=0.05, uncorrected. The vector for auditory condition described unexpected high-pitched sound as +1, expected high-pitched sound as -1, fixation cross as 0 and instructions as 0.

The statistical threshold for significance was p<0.05, FWE- corrected at voxel level. We performed t-tests to identify areas that show increased connectivity with the seed area in the condition of 1) all unexpected, compared with all expected, stimuli, 2) low-, compared with high-pitched sounds, 3) high-, compared with low-pitched sounds, 4) unexpected, compared with expected low-pitched sounds and 5) unexpected, compared with expected, high-pitched sounds. The contrast of expected, versus unexpected stimuli was not practical due to the difference in power (the number of expected stimuli was three times higher than the number of unexpected stimuli).

### 4.3.4. Results

#### 4.3.4.1. Behavioural data

No significant difference between reaction time to the down- or upward-pointing triangle was revealed by the repeated -samples test (t(11)=0.17, p=0.87 ). Reaction times were: mean 527.31 ms (SD 67.13) to upward pointing triangle and mean 525.13 ms (SD 79.65) to downward pointing triangle. Wilcoxon signed-rank test revealed no significant differences in the accuracy of responses between upward- and downward-pointing triangles (T=13, p=0.13). Accuracy was above 87%.

#### 4.3.4.2. FMRI results

The contrast of all experimental stimuli (expected and unexpected low-and high-pitched sounds) versus fixation cross baseline at p<0.01, uncorrected, included bilateral auditory cortex (Table 4.3) and served as the volume-of-interest (VOI) for subsequent corrected statistical comparisons.

Whole brain analysis

The contrast of all unexpected stimuli (low- and high-pitched sounds) versus all expected stimuli revealed no significant activations within the whole brain. No areas activated significantly more in response to unexpected low-pitched, compared with expected low-pitched sound, or in response to unexpected high-, compared with expected high-pitched sounds in the whole brain analysis. No significant activations were revealed in the contrast of low-, versus high-pitched sounds, or in the contrast of high-, versus low-pitched sounds in the whole brain analysis.

VOI analysis

The comparison of all unexpected stimuli (low- and high-pitched sounds) versus all expected stimuli (low-and high-pitched sounds) revealed no suprathreshold clusters within the VOI. No areas activated significantly in response to unexpected low-pitched sound, compared with expected low-pitched sound within the VOI. Contrast of unexpected, compared with expected, high-pitched sounds showed that activation in the left middle frontal gyrus (BA6) approached significance within the VOI (FWE-corrected p=0.075) (Table 4.4). Comparison of all (expected and unexpected) low-pitched sounds with all (expected and unexpected) high-pitched sounds revealed a significant activation in the right and left middle temporal gyri within the VOI (Table 4.4, Figure 4.6). No areas were activated significantly more by high-pitched than low-pitched sounds within the VOI.

#### 4.3.4.3. Effective connectivity results

In the analysis of effective connectivity in the condition of unexpected, versus expected, low-and high-pitched stimuli, as well as in the condition of low-pitched sounds versus high pitched sounds and in the condition of high-pitched sounds versus low-pitched sounds, the seed region was in the left STG (t=11.98, p<0.001, FWE-corrected in the whole brain, 2316 voxels, MNI coordinates: -46 -28 -2). Participant-specific seed-area was a voxel with the highest t-statistic in the area of the left superior and middle temporal gyrus. The contrast of unexpected (low- and high-pitched sounds) versus expected (low-and high-pitched sounds) revealed no significant activations in the whole brain or within the VOI. In the contrast of low-versus high-pitched sounds (expected and unexpected) right STG showed significantly increased connectivity with the seed area in the left STG in the whole brain analysis and within the VOI (Table 4.5, Figure 4.7). The contrast of high- versus low-pitched sounds revealed no significant activations, either in the whole brain analysis or within the VOI. The seed region for the analysis of connectivity in the condition of unexpected, versus expected, low-pitched sounds, was on the lower bank of the left STG (t=12.22, p<0.001 FWE-corrected in the whole brain, 2235 voxels, MNI coordinates: -46, -28, 0). Individual participants’ seed region was the area with the highest t-statistic in the left superior and middle temporal gyrus. The contrast of unexpected, versus expected, low-pitched sounds revealed that connectivity approached significance at voxel-level within the VOI in the following areas: the upper bank of the right STG (BA22) (Table 4.5) and right transverse temporal gyrus (BA 41) (Table 4.5).

The seed region for the analysis of connectivity in the condition of unexpected, versus expected, high-pitched sounds, was on the lower bank of the left STG (t=11.50, p<0.001 FWE-corrected in the whole brain, 2334 voxels, MNI coordinates: -46, -28, -2). Individual participants’ seed region was the area with the highest t-statistic in the left superior and middle temporal gyrus. The contrast of unexpected, versus expected, high-pitched sounds revealed that no areas showed increased connectivity with the seed area either in the whole brain or within the VOI.

**Table 4.3. Brain areas activated by experimental stimuli compared with fixation cross baseline.**

|  |  |  |  |
| --- | --- | --- | --- |
| Area | Peak *t* | MNI coordinates (*x y z*) | Cluster |
| Left hemisphere |  |  |  |
| STG | 11.98 | -46 -28 -2 | 3279 |
| Middle occipital gyrus | 3.89 | -44 -72 6 | 378 |
| Supramarginal gyrus | 3.90 | -40 -40 38 | 163 |
| Middle frontal gyrus | 3.73 | -32 0 56 | 127 |
| Cerebellum | 3.06 | -8 -54 -40 | 29 |
| Caudate nucleus | 2.87 | -14 16 12 | 51 |
| Inferior frontal gyrus | 2.70 | -28 28 2 | 10 |
| Parahippocampal gyrus | 2.60 | -34 -50 -6 | 6 |
| Precentral gyrus | 2.57 | -42 -4 46 | 8 |
| Right hemisphere |  |  |  |
| STG | 8.04 | 48 -28 8 | 3135 |
| Parahippocampal gyrus | 3.71 | 20 -42 -4 | 80 |
| Inferior frontal sulcus | 3.39 | 40 2 30 | 80 |
| Posterior cingulate | 3.22 | 20 -48 12 | 19 |
| Superior frontal gyrus | 3.04 | 12 48 44 | 16 |
| Middle frontal gyrus | 2.62 | 6 54 24 | 30 |

Areas where activation was significant in response to all experimental stimuli (expected and unexpected low- and high-pitched sounds) compared with the fixation cross baseline at p<0.001 uncorrected. Peak t = test statistic at the voxel showing greatest activity in a cluster. MNI – Montreal Neurological Institute. Cluster – number of voxels in a cluster at p<0.01, uncorrected.

**Table 4.4. Regions activated in experimental conditions.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Region (Brodmann area) | Peak *t* | FWE-*p* | MNI coordinates (*x y z*) | Cluster |
| L middle frontal gyrus (BA6)a | 3.92 | 0.075 | -26 -2 60 | 8 |
| R MTG (BA21)b  L MTG (BA21)b | 4.40  4.15 | 0.021  0.041 | 56 -12 -2  -54 -20 -8 | 48  30 |

Activations evoked by experimental conditions at statistical threshold of p<0.05 FWE (family-wise error) corrected, except for a), where p value is at trend level. Peak t = test statistic at the voxel showing greatest activity in a cluster. Cluster -number of voxels in a cluster at p<0.001, uncorrected. MNI- Montreal Neurological Institute. L- left, R- right.

1. Brain areas activated more at trend-level by unexpected, compared with expected, high-pitched tones within the volume of interest (VOI)
2. Brain areas activated significantly more by low-pitched tones (expected and unexpected), compared with high-pitched tones (expected and unexpected), within the volume of interest (VOI).

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**Figure 4.6. Areas activated significantly more by low-, compared with high-pitched, sounds.** Activation in the bilateral MTG (Table 4.4) are mapped on the saggital, coronal and axial surface (from left to right) of the SPM glass brain image within the volume of interest (VOI). Voxel threshold was p<0.05 FWE-corrected. SPM, statistical parametric mapping.

**Table 4.5. Effective connectivity of auditory cortex.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Brain area (Brodmann area) | Peak t | FWE-*p* | MNI coordinates (x y z) | Cluster |
| R STG (BA22)a | 11.52 | 0.016 | 58 -40 8 | 35 |
| R STG (BA22)b | 7.76 | 0.017 | 56 -38 6 | 22 |
| R STG(BA22)c | 6.00 | 0.071 | 46 -18 -2 | 17 |
| Right TTG(BA 41)c | 5.90 | 0.077 | 42 -34 10 | 27 |

Activations evoked by experimental conditions at statistical threshold of p<0.05 FWE (family-wise error) corrected. Peak t = test statistic at the voxel showing greatest activity in a cluster. Cluster -number of voxels in a cluster at p<0.001, uncorrected. MNI- Montreal Neurological Institute. L- left, R –right.

1. Brain areas where effective connectivity with auditory cortex was significantly greater in the condition of low-pitched tones (expected and unexpected) compared with high-pitched tones (expected and unexpected) in the whole brain analysis.
2. Brain areas where effective connectivity with auditory cortex was significantly greater in the condition of low-pitched tones (expected and unexpected) compared with high-pitched tones (expected and unexpected) within the volume of interest (VOI).
3. Brain areas where effective connectivity with left auditory cortex approached significance in the condition of unexpected, compared with expected, low-pitched tones within the volume of interest (VOI).

**E:\phd\theses\thesis\PPI low pitch versus high pitch.TIFFigure 4.7. Areas showing nearly significantly greater effective connectivity with auditory cortex in response to low-, compared with high- pitched sounds.** Activations in the right STG (Table 4.5) are mapped on the saggital, coronal and axial surface (from left to right) of the SPM glass brain image. Statistical threshold was p<0.05 FWE -corrected at voxel level. SPM- statistical parametric mapping.

### 4.3.5. Discussion

The fMRI Pitch Experiment employed a visuo-auditory associative learning paradigm with pairs of associated stimuli, where shapes cued auditory objects (low- and high-pitched tones). Activity in the left middle frontal gyrus approached significance in the condition of unexpected, compared with expected, high-pitched tones. This finding was not in line with the hypothesis, which predicted increased activity in the auditory cortex in response to surprising high-pitched tones. Contrary to hypothesis, which predicted no difference in auditory cortex in response to low-or high-pitched tones, bilateral MTG responded with significantly increased activity to low-pitched, compared with high-pitched, sounds. No areas activated significantly more in response to unexpected, compared with expected, low-pitched tones. This lack of increased activation was not in agreement with the hypotheses, which predicted increased response of auditory cortex to unexpected, compared with expected, auditory stimuli. As predicted, no area responded with increased activity to high-, compared with low-pitched sounds.

Significantly enhanced connectivity was found between left and right auditory cortex in STG in the condition of low-, compared to high-pitched sounds. This finding is not in line with the prediction of no difference in the auditory cortex modulation between the conditions of different pitch. The modulation of the left secondary auditory cortex by its right primary and secondary counterpart approached significance in the condition of unexpected, compared with expected, low-pitched tones. No areas showed significantly increased connectivity with auditory cortex (left STG) in response to unexpected, compared with expected, low- and high-pitched sounds. Our hypotheses predicted increased modulation of the auditory cortex by the prefrontal and visual cortices in these conditions. Finally, in line with the hypothesis, processing of high-, compared to low-pitched sounds was not associated with any significant connectivity.

The lack of increased activity in response to unexpected stimuli is not in line with the results of other studies investigating the processing of surprising perceptual objects. Previous neuroimaging research showed that stimuli that do not match prediction evoke increased activity in the cortical area specific to the modality of the stimulus (Opitz et al., 2002, den Ouden et al., 2009). It is thought that normal perception is based on predictive coding, in which higher cortical processing areas send a prediction of incoming input to the lower areas, which compare the expectation with actual external stimulus (Rao and Ballard, 1999). If the prediction is discrepant from the top-down signal, lower areas send a prediction error to the higher areas. Generating prediction error is thought to be reflected in the increase in neural activity ( Fletcher et al., 2001, Mitchell et al., 2003, Opitz et al., 2002 den Ouden et al., 2009).

One explanation for lack of significant increase in brain activity in response to tones of unexpected pitch in the current study could be that participants did not learn the associations and thus did not generate prediction error. However, the trend towards increased response to unexpected high-pitched sounds presented when a low pitch was expected in the BA 6 of the left middle frontal gyrus suggests some learning might have taken place. The trend-level increase in activity could be underpinned by a mechanism whereby the processing of a visual cue associated with the low-pitched sound might have triggered a retrieval of a cortical representation of that sound. When a high-pitched tone was presented instead, activity in the left middle frontal gyrus could have increased in response to a prediction error signal from auditory cortex. Brodmann area 6, including the middle frontal gyrus, has a role in planning movements, but also in visuo-spatial cognitive processes (Hanakawa et al., 2002, Lamm et al., 2001, Tanaka et al., 2005). It is, therefore, plausible, that this area is involved in perceptual cognitive operations such as processing of a prediction error signal. In addition, reduced activation in bilateral middle frontal gyri (BA 6 and 8) has been found in people at risk of psychosis relative to controls (Fusar-Poli et al., 2012). The expectation-perception model of auditory hallucinations (refer to Chapter 1) proposes that the ‘voices’, one of the symptoms of psychosis, could occur when prediction error generation and processing is insufficient. Hence, if the BA6 in the left middle frontal gyrus is part of the network processing unexpected auditory objects, the reduced activation in this area found in those at risk of psychosis could indicate impaired processing of auditory prediction error.

Increased activation of the bilateral MTG in response to low-, compared with high-pitched tones, could be due to differential response of the participants to sounds of different pitch. It has been shown that women prefer low-pitched male voices relative to high-pitched male voices (Smith et al., 2012). Hence, increased activation in MTG in response to low-pitched tones could underlie the greater preference in participants to these sounds, relative to high-pitched tones. Moreover, participants in Smith and colleagues’ study (2012) remembered better the pictures associated with the low-pitched male voices than pictures associated with either high-pitched male voices or female voices. The MTG is involved in integrating auditory and visual cues (Leitman et al., 2005). Hence, its increased activation in response to low-, relative to high-pitched tones might reflect enhanced learning of the association between the visual cue and the low-pitched tone, compared with learning of the association between the visual cue and the high-pitched tone. Therefore, it is plausible that increased activity in the bilateral MTG evoked by low-pitched sounds than by high-pitched sounds could underpin the preference for low-pitched tones and improved learning of their associations with the visual cues.

The involvement of the MTG in processing low-pitched sounds could also be related to processing the prosody i.e. the rhythm and intonation of speech, which allows to disambiguate vocal message and convey its affective aspects (Shea et al., 2007). Pitch (next to loudness and duration) is one of the main cues in recognizing prosody. Attention to prosodic affective cues activates MTG in healthy individuals (Mitchell et al., 2003). Hence, activation in this area could underpin the processing of low pitch as one of the cues in recognizing affective prosody.

Enhanced modulation of the left auditory cortex by its right counterpart during processing of low-compared with high-pitched tones, and unexpected, relative to expected, low-pitched tones could be due to the increased associative learning in trials containing low-pitched tones (Smith et al., 2012). Increased modulation of the left secondary auditory cortex by its right primary and secondary counterpart in response to unexpected low-pitched tones also suggests that activity in hierarchically lower processing level might influence activity in the higher processing levels within the auditory cortex when prediction needs to be updated.

The lack of increased response in auditory cortex to sounds of unexpected pitch could be due to the differences in the design. Sounds of different frequency utilized in MMN studies are presented more often (e.g. 2440 stimuli, compared with 48 in this study), at shorter intervals (every 500 – 1500 ms, as opposed to 12.5 s) and learning of the rules is based on repetition (Opitz et al., 2002, Mitchell et al., 2005, Kim et al., 2009). On the other hand, prediction-dependent responses were found in the FMRI Sound/Silence Experiment, where the acoustic difference between the auditory stimuli was greater. Therefore, it might be that when tones of different pitch are used, either the acoustic difference between them has to be larger in order to increase the contrast in the auditory cortex response, or the number of stimuli greater to increase sensory learning and the statistical power to detect the effect of learning.

## 4.4. General discussion (fMRI Sound/Silence and Pitch Experiments)

The perceptual processes have been explained in terms of predictive coding model, where each level in the processing hierarchy in the brain transmits an expectation of the incoming input to the lower level and the prediction signal to the higher level (Rao and Ballard, 1999). The expectation-perception hypothesis presented in this thesis proposes that a dysfunction of this process of comparing the prediction and actual stimulus might lead to insufficient prediction error and increased role of expectation in explaining external input. As a result, expected sounds could be misinterpreted as real auditory input, forming auditory hallucinations.

### 4.4.1. The findings

The current studies investigated how unexpected presence and absence of sound, as well as sounds of unexpected pitch affect neural activity in healthy individuals. Previous research showed that processing of unexpected stimuli is associated with increased activity in the stimulus-specific cortex (den Ouden et al., 2009, Fletcher et al., 2001). This increase is greater in response to unexpected presence than to unexpected absence of a stimulus (Fletcher et al., 2001). Enhanced activity in response to unexpected stimuli is thought to correspond to generating prediction error (den Ouden et al., 2009).

Results of the current studies suggest that a wide network of brain areas consisting of left middle and superior temporal gyri, left insula, left middle frontal gyrus and right STG could be involved in generating auditory prediction error. Left STG generates prediction error in response to unexpected sounds, but not silences, whilst left MTG generates auditory prediction error in response to both unexpected sounds and silences. A plausible explanation for the different pattern of response between STG and MTG to unexpected silence is that left STG specializes in processing sounds. Left MTG, on the other hand, could be higher in the hierarchy of the cognitive coding than left STG and its role could include interpreting activity or lack of it in the STG.

Increased activity in the left insula in response to unexpected, compared with expected sounds, indicate that this area is involved in processing surprising sounds when silence is expected. Significantly greater response of bilateral MTG to low-, relative to high-pitched sounds, suggests that activity in this area might underpin increased learning of associations between the visual cue and the low-pitched tone (Smith et al., 2012). Bilateral MTG could also be involved in processing low pitch as a prosodic cue (Mitchell et al.2003). Our results also suggest that activity in the left secondary auditory cortex is modulated by the right secondary auditory cortex in processing low-, compared with high-pitched sounds, and by the primary auditory cortex in processing unexpected, compared with expected, low-pitched sounds. It is plausible that areas that are lower in the cognitive hierarchy modulate areas that are higher when processing a prediction error.

### 4.4.2. A model of predictive coding in auditory hallucinations

Mismatch negativity, an index of updating auditory prediction, is attenuated in patients with schizophrenia (Umbricht et al., 2006). Such impairment could be due to the mechanisms such as abnormal PFC modulation of the thalamus (Barbas and Zikopoulos, 2007), abnormalities in the bottom-up pathways (Sweet et al., 2004; Sweet et al., 2007) and aberrant connectivity (Friston, 1998) (see Chapter 1 Sections1.5.2.1, 1.5.2.2, 15.2.3). Furthermore, STG appears to be hyperactive in hallucinating individuals (Allen et al., 2009, Shergill et al., 2000, Woodruff, 2004), possibly due to increased random, endogenous activity (Hunter 2006). Whilst physiological spontaneous activity in healthy auditory cortex can influence perception to a certain extent (Bernasconi et al., 2011), this effect is not large enough to affect the formation of a correct prediction error. Hyperactivity could, however, additionally reduce the responsivity of the auditory cortex to external auditory signals, consistent with the saturation hypothesis (Woodruff et al., 1997). The saturation hypothesis proposes that the ‘voices’ and perception or external speech share the same neural resources. Hence, hallucinating is associated with a reduced response of auditory cortex to external signals. It is plausible that when the expectation of the ‘voices’ is sent to STG, the neural representation of the prediction partially overlaps with networks of spontaneously hyperactive neurons (E1/S2, see Figure 4.8a). When external signal is a sound that does not match the expectation (S3), it is processed by limited neural resources due to the presence of expectation-related activity already enhanced by the random spontaneous activation (E1/S2). Such allocation of neural resources could lead to insufficient comparison of the external input with the prediction (PE3=E1/S2-S3). Similarly, when presented with silent input, the superior temporal gyrus would not be able to perform adequate comparison between external stimulus and the expectation. Due to the partial overlap between expectation- related activity and the random fluctuations, the signal sent from STG to MTG (PE0=E1/S2-S3, Figure 4.8b)would resemble, in some aspects, the STG response to sound. Such activation could be interpreted by MTG as reflecting a situation where external stimulation matches expectation more than is actually the case, resulting in the reduced prediction error often found in schizophrenia. For instance, if neurons in the area responsible for processing male voice are hyperactive, they might partially overlap with a network representing expectation of a threat. The resulting signal sent from auditory cortex could be interpreted by MTG as input that matches the prediction (e.g. an insult spoken in a male voice), thereby preventing the updating of predictive representations in the context of contradictory external information. Hence, a dysfunction of temporal cortex could lead to a failure in generating correct prediction error and to misconstruing of auditory expectation as a real sound. If the hallucinating person attempts to divert their attention from the ‘voices’ by, for example, listening to the music, expectation of sound might match the external stimulus (E1, Figure 4.8c). Similarly, if there is a pause in the hallucinated voices, an expectation of silence could be sent to the auditory cortex (E0, Figure 4.8d). In such cases the signal sent to MTG, would be consistent with the expectation and with the external stimulus (PE1=E1/S2-S1, Figure 4.8c and PE0=E0/S2-S0, Figure 4.8d).

Evidence suggests that grey matter volume in bilateral insula is reduced in men with schizophrenia who hallucinate, compared with those who have schizophrenia but do not hallucinate and with controls (Shapleske et al., 2002). Therefore, it is plausible that a dysfunction of the insula leads to impaired processing unexpected sounds and to insufficient prediction error. This, in turn, might result in exaggerated role of the top-down expectation in explaining auditory input.

The involvement of bilateral MTG in processing low-pitched sounds could be important in the genesis of auditory hallucinations. It has been shown that patients with schizophrenia have reduced ability to discriminate pitch in a tone-matching task (Leitman et al., 2005). This impairment was associated with deficits in recognizing different emotions, as well as emotion intensity, in vocal expressions. Unlike healthy individuals, patients were unable to use the pitch cues to recognize auditory emotions, although they had no difficulty utilizing cues based on loudness. Similar impairment in processing emotional prosody has been found in patients with schizophrenia suffering from auditory hallucinations (although not in patients without hallucinations) (Shea et al., 2007).

Attention to prosodic affective cues activates MTG in healthy individuals (Mitchell et al., 2003). The content of auditory hallucinations is often hostile, i.e. it consist of vulgar insults expressing anger and contempt (Nayani and David, 1996). It might be that a dysfunction of MTG leads to impaired ability to process prosody and, consequently, to exaggerated emotional expression in hallucinatory perceptions. In addition, the speaker in auditory hallucinations is most frequently male (Nayani and David, 1996). It has been shown that low frequency is an important cue to women in recognizing a natural male voice (Hunter et al., 2005). Taken together, this evidence suggests that overactivation of MTG might contribute to generation of false hostile utterances spoken in male voices in those suffering from auditory hallucinations.

**E1**

PE3=E1/S2-S3

**MTG**

**STG**

**S3**

PE3=E1/S2-S3

**PE3**

**a**

**E1**

PE0=E1/S2-S0

**MTG**

**STG**

**S0**

S2

**b**

**S2**

**S1**

**E1**

PE1=E1/S2-S1

**STG**

PE1=E1/S2-S1

**PE1**

**MTG**

**c**

**S0**

**E0**

PE0=E0/S2-S0

**STG**

S2

**MTG**

**d**

**S2**

**Figure 4.8. Model of auditory predictive coding in auditory hallucinations.**

a)Prediction: sound, external input: different sound, b) Prediction: sound, external input: silence, c) Prediction: sound, external input: matching sound (e.g. when a hallucinating person attempts to divert their attention from the ‘voices’ by listening to the radio) d) Prediction: silence, external input: silence (e.g. a pause in the running commentary). The division sign symbolizes the overlap of the neural networks representing expectation and spontaneous activity. PE in 4.8b<PE in 4.8a<PE in 4.8d<PE in 4.8c.

STG – superior temporal gyrus, MTG – middle temporal gyrus , S0- silent input from the ear, S2- excessive random endogenous activity in STG, S1- sound input from the ear (matching expectation), S3 – sound input from the ear (different from that expected), E1 – expectation of sound, PE0 – prediction error signalling silence, PE1, PE3- prediction error signalling sound.

### 4.4.3. Limitations and suggestions for future research

A potential limitation of the current studies is the small number of participants. In addition, the sparse-sampling scanning method employed, whilst optimal for auditory fMRI studies, also imposes limits to statistical analysis power by reducing the number of trials per unit scan time available with a particularly long TR. Future studies could benefit from employing greater number of trials and increased acoustic difference between the stimuli. Auditory prediction error in associative learning paradigms should also be investigated in individuals with auditory hallucinations. Since the content of the ‘voices’ is often salient and self-referential, elucidation of the effects of salience on auditory prediction error could also provide further insight into auditory processing and its abnormalities.

## 4.5. Conclusions (FMRI Sound/Silence and Pitch Experiments)

The different pattern of responding to unexpected silence in STG and MTG suggests that these areas form a hierarchy in auditory predictive coding. Significant increase in MTG activity in response to unexpected silence and lack of significant increase in STG response to the same stimuli suggests a specialization within the temporal cortex in the processing of auditory prediction error. It is plausible that STG generates prediction error in response to unexpected sounds, whilst MTG interprets STG activity and generates prediction error in response to both unexpected sounds and unexpected silence. Our results showing significantly enhanced activity in the left middle and superior temporal gyri, left insula, left middle frontal gyrus and right STG in response to unexpected auditory stimuli suggest that these areas could form a network processing auditory prediction error. Anatomical and functional abnormalities in this network, such as hyperactivity and reduced volume in STG (Woodruff et al., 1995, Barta et al., 1990), neural abnormalities in the feedforward pathways (Sweet et al., 2004, Sweet et al., 2007), aberrant connectivity (Friston, 1998, Kilpatrick et al., 2011) might lead to reduced processing of prediction error. The reduced error signal might fail to alter the expectation, leading to a situation where prediction is misconstrued as a real sound and to auditory hallucinations.

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# Chapter 5

# Expectation, salience and neural activity

**Abstract**

Adaptive behaviour requires the ability to predict emotionally neutral and potentially threatening stimuli, as well as the capacity to efficiently process and learn from events that deviate from the prediction. We propose that impaired processing of unexpected neutral auditory stimuli can lead to a situation where external stimuli fail to modulate predictions of threatening auditory percepts and expected sounds are erroneously perceived as real ones, leading to auditory hallucinations.

In this fMRI study we investigated normal auditory predictive coding mechanisms while manipulating the emotional salience of auditory stimuli. It was hypothesised that auditory cortex would show increased response to salient (here: threatening), compared with neutral, stimuli and to unexpected, compared with expected, auditory stimuli. Twelve healthy participants completed a task consisting of pairs of associated stimuli, where simple geometrical shapes were followed by neutral and salient words. Expected neutral and salient words were contrasted with their expected counterparts.

The increase in activity in the right posterior cingulate gyrus in response to unexpected neutral words (when the cue had previously been associated with salient words) approached significance. ACC showed significantly increased connectivity with auditory cortex in condition of salient, compared with neutral, words. There was no significant difference in neural activity in response to salient, compared with neutral words.

Our results suggest that the posterior cingulated cortex could be involved in generating prediction error and modulating response to neutral stimuli when salient stimulus is expected. Anterior cingulate cortex could modulate activity in the auditory cortex in response to salient stimuli. A dysfunction of these areas could therefore contribute to auditory hallucinations, where impaired processing of neutral stimuli and enhanced emotionally-laden modulation of the auditory cortex might lead to misconstruing of a threatening expectation as a real sound.

## 5.1. Introduction

Salience can be defined as a characteristic of a stimulus that attracts attention (Hogg and Vaughan, 2005). Emotional salience, in particular threatening nature, is one of the main characteristics of the auditory hallucinations [(Nayani and David, 1996)](#_ENREF_38). The expectation-perception model of the ‘voices’ presented in this thesis proposes that these false percepts arise as a result of abnormalities in the auditory predictive coding. Predictive coding model of perception (Rao and Ballard, 1999) describes a process in which expectation of an incoming input are generated by ‘higher’ brain areas and communicated to the ‘lower’ areas, which compare them with external input. In case of a discrepancy a prediction error signal is generated and sent to the higher areas. Processing of prediction error is associated with increase in neural activity in the stimulus-specific area, as well as connectivity between areas processing the cue and the outcome (den Ouden et al., 2009, Fletcher et al., 2001).

Evidence suggests that unexpected delivery of salient stimuli such as money reward or electrical stimulation when no outcome was expected, is associated with increased activity in the ventral striatum [(Jensen et al., 2007)](#_ENREF_171). When emotionally salient stimuli are presented next to neutral stimuli, processing of salient events is associated with greater activity in the stimulus-specific sensory cortex. For instance, emotional visual stimuli (spiders) evoked greater activity in visual cortex than neutral stimuli (disks) (Nahum et al., 2011). Similarly increased activity in response to emotionally salient stimuli (e.g. an applause or a screaming adult) compared to neutral sounds (e.g. ticking clock) was found in the auditory cortex [(Plichta et al., 2011)](#_ENREF_175). Enhanced neural response in auditory cortex was also associated with processing of syllables pronounced with emotional, compared with neutral, prosody [(Wiethoff et al., 2008)](#_ENREF_65). Such increase in activity evoked by salient stimuli might be due to priming of visual and auditory cortices by regions involved in processing emotions, especially amygdala, as well as prefrontal cortex, through feedback projections [(Amaral et al., 2003, Yukie, 2002, Plichta et al., 2011)](#_ENREF_175). Enhanced activity might improve perceptual discrimination [(Phelps et al., 2006)](#_ENREF_178), and detection of stimuli evoking fear [(Ohman and Mineka, 2001)](#_ENREF_179), thus modulating approaching and avoiding behaviour [(Lang, 1995)](#_ENREF_180).

Research investigating neural correlates of prediction error in processing salient sensory stimuli is scarce. Veldhuizen and colleagues (2011) found that unexpected salient event evoked greater increase in activity in sensory cortex than unexpected neutral event. Specifically, the increase in activity in primary taste cortex in the right anterior insula was greater for unexpected sweet taste (when a tasteless stimulus was expected) than for unexpected tasteless stimulus (when a sweet stimulus was expected). Such differential response in the stimulus-specific areas to breaches of expectation depending on the salience of the event was not found by Nahum and colleagues (2011). In a variant of a reversal learning task the visual cortex, OFC and parietal areas responded with increased activity when a visual target anticipated on the presented face was unexpectedly replaced by a non-target stimulus. This increase in activity was the same for unexpected spider (salient stimulus) and unexpected disk (neutral stimulus).

We propose that enhanced processing of threatening percepts and impaired processing of unexpected neutral auditory stimuli are important in the mechanism of auditory hallucinations. The expectation-perception model of auditory hallucinations proposes that the mechanisms underlying auditory hallucinations involve perceptual prediction of a threatening percept and impaired processing of prediction error. The predictions might have formed in the process of associating real auditory perceptions with feelings of threat. As a result of impairment in bottom-up transmission of signals discrepant from expectation and generating prediction error, the external stimuli fail to modulate the perceptual expectation. Consequently, prediction might be perceived as a real, external sound, leading to auditory hallucinations. Pairing of visual and auditory stimuli served in this study as a model for the development of internal associations, which could underlie auditory hallucinations.

The current study employed a task consisting of pairs of associated neutral and salient stimuli in order to investigate processing of auditory prediction error in the context of emotional salience. It was hypothesised that changes in activity in response to unexpected outcomes depend on the salience of the stimuli. According to **hypothesis 1)** salient stimuli would evoke greater activity in the auditory cortex than neutral stimuli. **Hypothesis 2)** stated that unexpected salient stimuli (salient words where the visual cue had been previously associated with a neutral word) would evoke greater activity than expected salient stimuli. **Hypothesis 3)** predicted that unexpected neutral stimuli (neutral words where the visual cue had been associated with salient words) would evoke greater activity than expected neutral stimuli. Finally **hypothesis 4)** stated that the increase in response to unexpected stimuli would be greater for salient, compared with neutral, words.

We also investigated the effect of expectation and salience on effective connectivity, i.e. the causal influence of activity in some areas on activity in the auditory cortex. Specifically, we aimed to elucidate which areas would show significantly enhanced connectivity with auditory cortex in conditions of 1) unexpected, compared with expected, words, 2) neutral, compared with salient words, 3) salient, compared with neutral words, 4) unexpected, compared with expected, neutral words and 5) unexpected, compared with expected, salient words.

Generating prediction error could be underpinned by enhanced effective connectivity between areas processing the cue and the outcome [(den Ouden et al., 2009)](#_ENREF_14). Prefrontal cortex activates in response to a sound deviating from other sounds (mismatch negativity, considered to reflect updating of predictions (Winkler, 2007, Schall et al., 2003) as well as modulates activity of the regions involved in processing predicted events (McIntosh et al., 1998). Therefore, **hypothesis 5)** predicted that visual and prefrontal cortex would show significantly increased effective connectivity with auditory cortex in the condition of unexpected neutral and salient words. **Hypothesis 6)** stated that visual and prefrontal cortices could show significantly increased connectivity with auditory cortex in response to unexpected, compared with expected, neutral words.

Evidence suggests that posterior insula, orbitofrontal cortex (OFC) and ACC respond with increased activity to affectively negative words and anxiety-provoking sounds (Lewis et al., 2007, Frey et al., 2000). Hence, **hypothesis 7)** stated that processing of salient words could be associated with increased effective connectivity of the posterior insula, OFC and ACC with auditory cortex. **Hypothesis 8)** stated that the visual, prefrontal (including orbitofrontal) cortex, as well as ACC and posterior insula would respond with significantly increased connectivity with auditory cortex to unexpected, compared with expected, salient words. Finally, **hypothesis 9)** predicted that no areas would show increased effective connectivity with auditory cortex in processing of neutral, compared with salient words.

## 5.2. Method

For information on participants, questionnaires, general procedure, scanning and data preprocessing, refer to Chapter 2, Sections 2.4.1, 2.4.2, 2.4.3., 2.4.4 and 2.4.5.

### 5.2.1. Stimuli

Stimuli were presented using commercially available ‘Presentation’ software (Neurobehavioral Systems, Albany, USA, [www.neurobs.com](http://www.neurobs.com)). In the acquisition stage visual stimuli were presented on a computer screen and auditory stimuli were delivered over the headphones. In the mismatch phase, conducted in the scanner, visual stimuli were presented via a projector-screen system with a mirror fitted over the radiofrequency head coil and auditory stimuli were delivered via a MRI compatible sound system over the headphones. Visual stimuli consisted of a square and a diamond, unfilled, white and presented on the black background. The word ‘sort’ was matched with regard to frequency [(Kucera and Francis, 1967)](#_ENREF_188), number of syllables and grammatical part of speech with the word ‘kill’ and the word ‘fold’ was similarly matched with the word ‘hate’. Words were printed in printed in white font on a black background. The words were recorded in a male voice in open source software (Audacity programme: [www.audacity.sourceforge.net](http://www.audacity.sourceforge.net)) and used as auditory stimuli. A static white fixation cross was presented in the centre of the black background as a baseline in the mismatch phase.

### 5.2.2. Procedure

For the general overview of the procedure refer to Chapter 2 section 2.4.3. The experiments consisted of two phases: acquisition of contingencies and mismatch.

**Acquisition phase**

The aim of the acquisition phase was to induce learning of associations between the visual and auditory stimuli. The acquisition phase took place in a quiet room and consisted of 60 trials. Learning of complex association rules have been noted after 15-20 trials conforming to the contingency (Bendixen et al., 2008). Sparse-sampling method of neuroimaging requires a relatively long time between consecutive trials (12.5 s). Therefore, the number of trials in the current study did not exceed that employed by other fMRI investigations of neural correlates of prediction error (Corlett et al., 2004, 2007, Menon et al., 2007). Unbeknownst to the participants, a square was always followed by a salient word: ‘kill’ (15 trials) or ‘hate’ (15 trials). In the remaining 30 trials diamond was always followed by a neural word: ‘sort’ (15 trials) or ‘fold’ (15 trials). The order of the trials was randomized. The structure of each trial was as follows: a single shape (either a diamond or a square) was followed by a pair of shapes (a diamond and a square, side-by-side) (Figure 5.1). After participants indicated whether the initially presented shape appeared on the left or on the right from the centre of the screen, a spoken word was presented. Simultaneously with auditory events, the words ‘kill’ and ‘sort’ or ‘hate’ and ‘fold’ were presented and remained on the screen until participants indicated whether the text corresponding to auditory stimulus was on the right or on the left. The words on the screen were always in pairings ‘kill’ -‘sort’ and ‘hate’ -‘fold’ in order to enhance the contrast between a salient and a neutral word. Trials were separated by 1 s. Responses ensured that participants paid attention to the stimuli. This stage took approximately 5 minutes, depending on the speed of participants’ response.

kill sort



500 ms

500 ms

Until response detected

Until response detected

Until response detected

500 ms

500 ms

Until response detected

500 ms



500 ms

hate fold

‘sort’ or ‘fold’

‘kill’ or ‘hate’

**Figure 5.1.Task design in the acquisition phase.** Participants responded to both visual and auditory stimuli. The square and the diamond appeared simultaneously side-by-side and remained on the screen until response was detected. Participants pressed the right arrow key if the shape on the right from the centre of the screen corresponded to the previously presented single shape and the left arrow key if the shape on the left from the centre of the screen corresponded to the previously presented single shape. In the mismatch phase, designed to contrast expected with unexpected outcomes, participants pressed the second button on the response box with their index finger if the target shape was on the left from the centre of the screen, and the third button on the response box with their middle finger if the target shape was on the right from the centre of the screen. Response to the sound , required only in the acquisition phase was cued by words ‘kill’ and ‘sort’ (after a square) or ‘hate’ and ‘fold’ (after a diamond) appearing in the centre of the screen simultaneously with auditory events until response was recorded. Participants pressed the right arrow key when the word on the right from the centre of the screen corresponded to what they heard and the left arrow key if the word on the left from the centre of the screen corresponded to what they heard. Position of the shapes and words on the screen was randomized

**The mismatch phase**

The mismatch phase was completed in the scanner and took form of a mixed design. In this phase expected neutral and salient words were contrasted with unexpected neutral and salient words. In 25% of the trials the cues were followed by unexpected outcome, i.e. a square was followed by a neutral word (‘sort’ or ‘fold’) and a diamond was followed by a salient word (‘kill’ or ‘hate’). The refresher session before the scanning commenced presented participants with 10 repetitions of the pairs containing neutral word: a diamond followed by the word ‘sort’ (5 trials) or ‘fold’ (5 trials) and 10 repetitions of the pairs containing a salient word: square followed by the word ‘kill’ (5 trials) or ‘hate’ (5 trials). These trials were presented in randomized order and participants responded to both visual and auditory stimuli. The refresher was followed by 3 blocks of 16 experimental trials (48 trials altogether) interspersed with 2 blocks of 8 baseline (fixation cross) trials (16 baseline trials altogether). Each block of 16 trials consisted of the following visual-auditory parings: 3 pairs of diamond-‘fold’ and 3 pairs of diamond –‘sort’ (6 expected neutral outcomes), 3 pairs of square ‘’hate’ and 3 pairs of square –‘kill’ (6 expected salient outcomes), 1 pair of square –‘sort’, 1 pair of square-’fold’ (2 unexpected neutral outcomes), 1 pair diamond-‘kill’ and 1 pair diamond-‘hate’ (2 unexpected salient outcomes). The order of the trials was pseudo-randomized so that the unexpected auditory stimuli did not appear in the first 4 trials. The pause between presentation of the pair of shapes and an auditory stimulus was set at 750 ms. Unlike in the acquisition phase, participants were not required to respond to the sounds. Each baseline block consisted of 8 presentations of fixation cross, to which participants responded by pressing the second button on the response box with their index finger. The fixation cross appeared at the same time point as the pair of shapes in the experimental blocks to control for the motor response. The first time-point of each block presented participants with instructions as to the task they should perform during that block. This part of experiment took 14 min 45s.

### 5.2.3. Data analysis

#### 5.2.3.1. Behavioural analysis

Response time to shapes was recorded in tens of milliseconds, converted to milliseconds and analyzed.

#### 5.2.3.2. FMRI analysis

Data was analysed with voxel-wise GLM. First, contrasts were estimated at the single-participant level. These estimates were then entered into the second level, random- effect model. In the group level analysis participant and condition were modelled as predictors using flexible factorial design. Non-independence of images from the same participant and unequal variance between conditions and participants were assumed. We identified voxels which responded to all stimuli (all expected and unexpected neutral and salient words) versus fixation cross baseline at p<0.01, uncorrected. These voxels then formed the volume- of- interest (VOI) for subsequent statistical corrections. Next, we performed t-tests to compare unexpected (neutral and salient) with expected (neutral and salient) words. This was followed by comparison, using t-tests, of unexpected and expected neutral words and unexpected and expected salient words. We also employed t-tests to contrast neutral with salient words and salient with neutral words. All contrasts were performed in the whole brain analysis and within the VOI. Each contrast was performed in the whole brain analysis and within the VOI. The voxel-level statistical threshold for reporting was p<0.05, family-wise-error (FWE) corrected. MNI coordinates were converted to Talairach and Tournoux space using the mni2tal software routine in Matlab. Anatomical locations were identified using the Talairach and Tournoux paper atlas [(1988)](#_ENREF_159).

#### 5.2.3.3. Effective connectivity fMRI analysis

The first part of the effective connectivity analysis aimed to identify areas showing significantly increased connectivity with the auditory cortex in the condition of unexpected, compared with expected words and in the condition of salient and neutral words. For this purpose the seed region was identified as the maximum activation voxel in the group contrast of all experimental stimuli versus fixation cross baseline at p=0.001, uncorrected. We searched individual participants’ contrast images of all experimental stimuli versus fixation cross, displayed at p<0.05, for a voxel with highest *t* statistics in the area of the group seed. This voxel was the participant-specific seed region. The first eignevariate of the time-course data was extracted from the 5-mm sphere with the seed regions as the centre for each participant. The mean value of the eignevariate was then subtracted from each time point value, creating a time course vector with 69 time points (the physiological variable).

Parametric connectivity contrast images were produced in the first-level analysis for every participant with the goal of identifying areas that show increased connectivity with the seed area in the condition of unexpected, versus expected, stimuli. First, the time-course vector was multiplied with the vector representing the condition (the psychological variable). The condition vector was represented by values: unexpected words (+1), expected words (-1), fixation cross (0), instructions (0). The multiplication generated the physiological interaction term (PPI; Friston et al., 1997). The PPI term was then entered into the first-level analysis as an effect of interest. The time course of the seed area and the condition were entered as effects of no interest. The first-level analysis generated parametric connectivity contrast images for each participant’s scans. These contrast images were then entered into a group-level analysis in a flexible factorial model with participant and condition as factors.

Parametric connectivity contrast images were also produced for each participant in order to identify areas that show increased connectivity with the seed area in the condition of salient, versus neutral and neutral, versus salient, words. In the first-level analysis the psychophysiological interaction term (PPI) was produced by multiplying the time-course vector with the condition vector: salient word (+1), neutral word (-1), fixation (0), instructions (0). The PPI term was entered as an effect of interest. The time course and the condition were entered as effects of no interest. The first-level analysis generated parametric connectivity contrast images for each participant’s scans. These contrast images were then entered into a group-level analysis in a flexible factorial model with participant and condition as factors.

Next step involved analysis of the connectivity in the condition of unexpected, versus expected, neutral words. The seed was identified as the voxel of maximum activation in the group contrast of all neutral words (expected and unexpected) versus fixation cross baseline at p=0.001, uncorrected. We then searched individual participants’ contrasts images of all neutral words versus fixation cross displayed at p<0.05 for a voxel with highest *t* statistics in the area of the group seed. This voxel was the participant-specific seed region. The condition vector was described as follows: unexpected neutral word (+1), expected neutral word (-1), fixation cross (0) and instructions (0). The first- and second-level analysis followed as described above.

Effective connectivity was also analyzed in the condition of unexpected salient words compared with expected salient words. The seed was identified as the maximum activation voxel in the group contrast of all salient words (expected and unexpected) versus fixation cross baseline at p=0.001, uncorrected. The participant-specific seed region was identified by searching individual participants’ contrasts images of all salient words versus fixation cross displayed at p<0.05 for a voxel with the highest t statistics in the area of the group seed. The condition vector was described as follows: unexpected salient word (+1), expected salient word (-1), fixation cross (0) and instructions (0). The first- and second-level analysis followed as described above.

The voxel-level statistical threshold for significance was p<0.05, FWE- corrected. We performed t-tests to identify areas that show significantly increased activity with the seed area in the condition of unexpected, compared with expected, neutral and salient words. The inverse contrast was not practical due to the difference in power (the number of expected stimuli was three times higher than the number of unexpected stimuli). We also conducted t-tests to find areas that showed significantly increased connectivity with the seed area in the condition of neutral, versus salient words, and in the condition of salient, versus neutral words. Parametric connectivity contrasts were generated, using t-tests, for unexpected neutral words compared with expected neutral words and for unexpected salient words compared with expected salient words.

## 5.3. Results

### 5.3.1. Behavioural results

A within samples t-test revealed no significant difference between reaction time to a diamond (mean 434.98, SD 15.68) and a square (422.23, SD 14.69) (t(11)= -1.5, p=0.16). Wilcoxon signed rank test revealed no significant difference in accuracy of responses to square (mean 97.22, range 4.1) diamond (median 100, range 4.17) (Z=-0.88, p=0.38).

### 5.3.2. FMRI results

Areas revealed in the contrast of all experimental stimuli (expected and unexpected neutral and salient words) versus fixation cross baseline (see Table 5.1) at p<0.01, uncorrected, included auditory cortex and served as the brain VOI for subsequent family-wise error (FWE)-corrected statistical comparisons. This contrast revealed that activation in response to words in the right auditory cortex was greater than in the left auditory cortex.

Whole brain analysis

There was no significant activation in the whole brain analysis in response to all (expected and unexpected) neutral versus all salient words. Increase in activity in the right posterior cingulate gyrus in response to unexpected neutral words compared with expected neutral words approached significance in the whole brain analysis (Table 5.2, Figure 5.2). The response to unexpected and expected salient words was similar. The contrast of all salient versus all neutral words and the contrast of all neutral versus all salient words revealed no significant activations in the whole brain analysis.

**Table 5.1. Brain areas activated by all experimental stimuli compared with fixation cross baseline.**

|  |  |  |  |
| --- | --- | --- | --- |
| Region | Peak *t* | MNI coordinates (*x y z*) | Cluster |
| Left hemisphere |  |  |  |
| MTG | 9.46 | -50 -26 -6 | 3158 |
| Precentral gyrus | 4.90 | -30 -8 56 | 2923 |
| Superior frontal sulcus | 3.96 | -6 8 56 | 219 |
| Parahippocampal gyrus | 3.27 | -16 -40 -6 | 209 |
| Precuneus | 3.12 | -12 -66 26 | 97 |
| Cerebellum | 3.16 | -10 -72 -34 | 95 |
| Lingual gyrus | 2.89 | -22 -78 -8 | 39 |
| Insula | 3.13 | -40 22 6 | 35 |
| Middle occipital gyrus | 3.16 | -36 -72 -2 | 25 |
| Cingulate gyrus | 3.08 | -16 -42 34 | 20 |
| Posterior cingulate gyrus | 2.70 | -16 -54 -16 | 15 |
| Inferior frontal gyrus | 2.50 | -44 24 -12 | 10 |
| Right hemisphere |  |  |  |
| STG | 10.31 | 44 -18 0 | 5252 |
| ACC | 4.85 | 22 -2 38 | 1464 |
| Cerebellum | 4.17 | 22 -68 -48 | 356 |
| Precuneus | 3.58 | 10 -70 28 | 581 |
| Middle frontal gyrus | 3.79 | 32 -8 64 | 144 |
| Cingulate gyrus | 3.49 | 6 -50 44 | 74 |
| Inferior temporal gyrus | 2.81 | 56 -62 -10 | 54 |
| Inferior frontal gyrus | 2.88 | 46 32 -8 | 42 |
| Posterior cingulate gyrus | 3.08 | 8 -32 22 | 41 |
| Inferior occipital gyrus | 2.72 | 36 -68 -10 | 31 |
| Parahhipocampal gyrus | 2.88 | 36 -20 -18 | 10 |

Regions where activation was significant in response to all experimental stimuli (expected and unexpected sounds and silences) at p<0.01 uncorrected. Peak t = test statistic at the voxel showing greatest activity in a cluster. MNI – Montreal Neurological Institute. Cluster = number of voxels activated at p < 0.001, uncorrected, in a cluster.

VOI analysis

There was no significant activations within the VOI in response to all (expected and unexpected) neutral versus all salient words. No areas activated significantly in response to unexpected, compared with expected, neutral words within the VOI. There was no significant response to unexpected, compared with expected salient words within the VOI. The contrast of all salient versus all neutral words and the contrast of all neutral versus all salient words revealed no significant activations within the VOI.

### 5.3.3. Effective connectivity analysis.

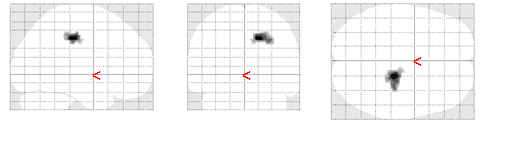
The seed are for the analysis of effective connectivity in the condition of unexpected, versus expected stimuli, as well as neutral versus salient words and salient versus neutral words was on the upper bank of right STG (t=10.31, p<0.001, uncorrected, 3475 voxels, MNI coordinates: 44 -18 0). The participant-specific seed region was a cluster with highest *t*-statistic in the right STG or MTG.

**Table 5.2: Brain areas that activated significantly in experimental conditions.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Region (Brodmann Area) | Peak *t* | FWE-*p* | MNI coordinates (*x y z*) | Cluster |
| R posterior CG (BA 31)a | 5.29 | 0.055 | 16 -24 42 | 326 |
| L anterior CG (BA 24)b | 10.62 | 0.034 | -10 4 34 | 68 |

CG – cingulate gyrus. Peak t = test statistic at the voxel showing greatest activity in a cluster. Cluster- number of voxels activated at p<0.001, uncorrected. MNI- Montreal Neurological Institute. L- left, R –right.

1. Brain area where an increase in activity neared significance in response to unexpected, compared with expected neutral words at p<0.05 corrected for family-wise error (FWE) in the whole brain analysis.
2. Brain area showing significantly increased effective connectivity with auditory cortex in response to salient, compared with neutral words at p< 0.05 FWE-corrected in the whole brain analysis.

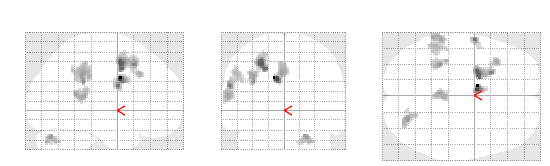


**Figure 5.2. Brain area where increase in activation approached significance in the condition of unexpected, compared with expected, neutral words**. Activation in the right posterior cingulate cortex (Table 5.2) is mapped on the saggital, coronal and axial surface (from left to right) of the SPM glass brain image within the VOI. Voxel threshold was p<0.05 FWE-corrected. SPM, statistical parametric mapping.

Left anterior cingulate cortex showed significantly increased connectivity with the seed region in the auditory cortex in the contrast of salient (expected and unexpected) versus neutral (expected and unexpected) words in the whole brain analysis (Table 5.2, Figure 5.3).

The contrast of unexpected (neutral and salient) words versus expected words revealed no areas showing increased effective connectivity with the seed area in the whole brain analysis or within the VOI. No areas showed increased effective connectivity with the seed area in the contrast of neutral (expected and unexpected) versus salient (expected and unexpected) words either in the whole brain or within the VOI.

The seed for the analysis of effective connectivity in the condition of unexpected, versus expected neutral words was on in the right posterior insula near STG (t=10.04, p<0.001, uncorrected, 3373 voxels, MNI coordinates: 44 -18 0). The participant-specific seed area was a cluster with highest *t*-statistic in the right posterior insula, STG and MTG. The contrast of unexpected, versus expected neutral words revealed no significant activations either in the whole brain analysis or within VOI. The seed for the analysis of effective connectivity in the condition of unexpected, versus expected salient words was the same as that for the condition of unexpected, versus expected neutral words. There were no significant activations in the whole brain analysis and no suprathreshold activations within the VOI in response to unexpected, compared with expected, salient words.



**Figure 5.3. Brain area which showed significantly increased connectivity with auditory cortex in condition of salient, compared with neutral, words.** Activation in the left anterior cingulate cortex in the whole brain analysis (Table 5.2) is shown in the red circle and is mapped on the saggital, coronal and axial surface (from left to right) of the SPM glass brain image. Voxel threshold was p<0.05 FWE-corrected. SPM, statistical parametric mapping.

## Discussion

This study employed an associative learning task in fMRI to investigate neural correlates of expected and unexpected neutral and salient spoken words in healthy individuals. Increase in the activation of the right posterior cingulate gyrus in response to unexpected, compared with expected, neutral words, approached significance. No areas responded with significantly increased activity to unexpected, compared with expected, salient and neutral words. Activity in response to expected and unexpected salient words was also similar. There were no significant differences in brain activity in response to salient, relative to neutral words. These findings were not in line with the hypotheses, which predicted enhanced response in the auditory cortex to unexpected, compared with expected, and salient, relative to neutral, stimuli. Auditory response to experimental stimuli (words) compared with baseline was greater in the right than in the left auditory cortex.

In line with the hypothesis, ACC modulated activity in the auditory cortex in response to salient, compared to neutral words. The other hypothesised regions – the OFC and posterior insula – did not show such increased connectivity. There were no differences in connectivity when unexpected, compared with expected, words were presented, regardless of their salience. This finding was in disagreement with the hypotheses, which predicted increased modulation of auditory cortex by the prefrontal and visual cortex. Finally, in line with the hypotheses, no areas appeared to modulate activity in auditory cortex in response to neutral, compared with salient words.

The ability to predict and to prepare a response to salient events is important for survival as it stimulates approach to appetitive stimuli and avoidance of aversive stimuli (Lang, 1995). According to the predictive coding model of perception, the brain generates predictions of incoming stimulus on the basis of prior knowledge and experience (Rao and Ballard, 1999). The prediction is compared with the external input and in case of discrepancy a prediction error signal is generated. It signifies a change in environment or a failure in learning, which might be important to survival (Bubic et al., 2010). Consequently, future expectations are modified according to the state of the external environment.

Generation of prediction error is thought to correspond to increased neural activity found in response to unexpected stimuli (den Ouden et al., 2009). Emotionally salient stimuli induce increased response in the stimulus-specific cortex compared with neutral stimuli, e.g. spiders compared with disks in visual cortex (Nahum et al., 2011) and an applause compared with ticking clock in the auditory cortex (Plichta et al., 2011). However, evidence in the area of predictive coding in the context of emotional salience is scarce and equivocal. The increase in response to unexpected salient stimuli was shown to be greater in the Veldhuizen and colleagues’ study (2011), but in the Nahum and colleagues (2011) there was no difference between response to unexpected salient and unexpected neutral outcomes.

The trend-level increase in the response of the right posterior cingulate gyrus suggests that this area could be part of the network processing auditory prediction error. In line with this interpretation, posterior cingulate gyrus was shown to respond with increased auditory event-related potential to a spoken word when it was a deviant compared to the same word when it served as a control stimulus (i.e. occurring with the same probability as any other stimulus in the sequence) (Laufer et al., 2009). This area has also been shown to activate in anticipation of distracters (to-be-inhibited stimuli) (Ciesielski et al., 2011). The increased response was reduced in those suffering from obsessive-compulsive disorder, a condition underpinned by constant anticipation of threatening events. When a salient word is expected and a neutral word presented instead, a potential response prepared in anticipation of a salient stimulus might have to be inhibited. Therefore, it is plausible that processing of unexpected neutral words and anticipating a distracting stimulus are underpinned by similar inhibitory processes. Auditory hallucinations are often characterized by threatening content (Nayani and David, 1996). The expectation-perception hypothesis proposes that the ‘voices’ are expected percepts insufficiently modulated by prediction error. Hence, it could be that the anticipation of the threatening events that is a feature of the obsessive-compulsive disorder, also occurs in those experiencing auditory hallucinations. Reduced activity in anticipation of distracting or in response to non-salient stimuli in the posterior cingulated gyrus could, therefore, contribute to the enhanced expectation of the threatening ‘voices’.

Enhanced connectivity of the anterior cingulate with the auditory cortex in response to salient, compared with neutral, words is in line with the evidence indicating that this area is involved in processing emotional stimuli (Bush et al., 2000). The severity of the positive symptoms has been shown to be associated with increased resting activation and metabolism of ACC (Cleghorn et al., 1990, Lahti et al., 2006). The anterior cingulate also tends to activate in those prone to hallucinations when they are hypnotized and either hear or hallucinate a word (Szechtman et al., 1998). Such activation was not found in controls. The authors suggest that auditory attention in voice hearers could be modulated by emotion more than it is the case in healthy controls. In addition, those who hallucinate showed increased correlations of activity between ACC and left superior temporal cortex relative to non-hallucinating patients and healthy controls (Cleghorn et al., 1990). This evidence suggests that in schizophrenia ACC could modulate activity in auditory cortex in such a manner that a perception of emotionally-laden auditory stimuli would be more likely to arise from endogenous activity.

The stronger activation in the right than the left auditory cortex in response to words is inconsistent with the evidence suggesting that in the majority of right-handed individuals language processing is lateralized to the left hemisphere (Knecht et al., 2000). Such altered lateralization might be due to stress. It has been shown that presentation of threatening words reverses the normal right visual field (left hemisphere) advantage in males due to the increased right hemisphere activation (Van Strien and Morpurgo, 1992). In another study moderate stress (impending examination) changed right visual-field advantage to left visual-field advantage in a divided visual field lexical task, compared with non-stressful situation (Gruzelier and Phelan, 1991). This reversal was also due to improved right hemisphere performance. In the current study stress might have resulted from the noisy and claustrophobic nature of fMRI environment, the length of the scanning session and the threatening nature of some of the stimuli (the words ‘kill’ and ‘hate’).

Lack of increased response to salient, compared with neutral words is similar to Sanjuan and colleagues’ (2007) finding, but in contradiction of evidence that suggests enhanced auditory activity associated with salient stimuli such as screaming or syllables pronounced with emotional prosody [(Plichta et al., 2011](#_ENREF_175), [Wiethoff et al., 2008)](#_ENREF_65). A plausible explanation for the lack of difference in response to neutral and salient words is that the dissimilarity in the emotional meaning of the words chosen as neutral and as salient was insufficient. However, connectivity between ACC and auditory areas in response to words ‘kill’ and ‘hate’ relative to the words ‘sort’ and’fold’ was significantly increased. Since ACC is involved in processing emotional stimuli (Bush et al., 2000), this finding suggests that the words ‘kill’ and ‘hate’ were more salient than the words ‘sort’ and ‘fold’. However, it could be that words with meaning that is more self-referential and relevant to culture, particularly of student population, such as ‘failure’ or ‘loser’ are more emotionally salient than words used in the current study and their processing would be associated with greater differences in brain activity. A measure of affective judgment of the employed stimuli could be useful in future research.

The absence of increased response to unexpected, compared with expected words in the auditory cortex might be due to insufficient acoustic difference between the stimuli and the noisy environment of the MRI scanner. Future studies could investigate further predictive coding underlying processing of salient stimuli by utilizing more self-referential salient words.

In conclusion, results of the current study suggest that the posterior cingulate gyrus could play a role in generating auditory prediction error and inhibiting inappropriate response when a neutral stimulus violates the expectation of a salient stimulus. Therefore, dysfunction of this area might contribute to the presence of auditory hallucinations, where auditory prediction is typically salient and processing of unexpected neutral stimuli could be impaired. The current study also provides further evidence that ACC is part of the network processing emotionally salient stimuli. Hence, increased activity in this area often found in those experiencing auditory hallucinations could contribute to the generation of salient auditory stimuli from endogenous activity.

## Chapter 6

# Analysis of the combined data from fMRI Sound/Silence, Pitch and Salience Experiments

**Abstract**

This chapter describes the results of the analysis of the combined data from FMRI Sound/Silence, Pitch and Salience Experiments. These studies employed an associative learning task where a visual cue induced learning of an auditory expectation. It was hypothesised that unexpected, versus expected stimuli (silence, sound, low-and high-pitched tones, neutral and salient words) would evoke significantly greater response in the auditory cortex. The results revealed a significantly increased activity in the bilateral lingual gyri and in the left hippocampus in response to unexpected, versus expected, auditory events. These findings suggest that when a prediction is induced by associating a cue with an auditory outcome, expectation modulates neural activity in the area, which processes the cue, allowing the updating of its validity. Increased hippocampal activity indicates the involvement of this area in the comparison of the expectation derived from the representations stored in memory with the current sensory input.

## 6.1. Aims and hypotheses

The analysis described in chapter aimed to elucidate the neural mechanisms of auditory predictive coding. The fMRI Sound/Silence, Pitch and Salience Experiments employed associative learning tasks where a visual cue was followed by an auditory outcome and expected auditory events were contrasted with unexpected ones. It was hypothesised that all unexpected auditory outcomes (silence, sounds, low- and high-pitched tones, neutral and salient words) would evoked significantly greater activity in the auditory cortex than their expected counterparts.

## 6.2. Method

For the information about the participants, questionnaires employed, the general procedure, scanning and data preprocessing – refer to Chapter 2, Sections 2.4.1, 2.4.2, 2.4.3., 2.4.4 and 2.4.5.

For the description of the stimuli and experiment specific procedure – refer to method in Chapter 4 (Sections 4.2.3.1., 4.2.3.2, 4.3.3.1., 4.3.3.2) and Chapter 5 (Sections 5.2.1 and 5.2.2).

Data from FMRI Sound/Silence, Pitch and Salience Experiments were analysed with voxel-wise GLM. Estimates from the single-participant level were entered into the second level, random- effect model. Participant, condition and scan session were modelled as predictors using flexible factorial design. Non-independence of images from the same participant and unequal variance between conditions and participants were assumed. We identified voxels which responded to all experimental stimuli (all expected and unexpected silences, sounds, low-and high-pitched tones, neutral and salient words) versus fixation cross baseline at p<0.01, uncorrected. These voxels then formed the volume- of- interest (VOI) for subsequent statistical corrections. Next, we performed t-tests to compare unexpected (silence, sound, low- and high-pitched tones, neutral and salient words) with their expected counterparts. Each contrast was performed in the whole brain analysis and within the VOI. The voxel-level statistical threshold for reporting was p<0.05, family-wise-error (FWE) corrected. MNI coordinates were converted to Talairach and Tournoux space using the mni2tal software routine in Matlab. Anatomical locations were identified using Talairach and Tournoux atlas [(1988)](#_ENREF_159).

**Table 6.1. Brain areas activated by all experimental stimuli from fMRI Sound/Silence, Pitch and Salience Experiments combined, versus fixation cross baseline.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Region** | **Peak *t*** | **MNI coordinates (*x y z*)** | | **Cluster** |
| Left hemisphere |  | |  |  |
| STG | 8.65 | | -46 -32 2 | 3486 |
| Inferior parietal lobule | 4.89 | | -28 -60 48 | 583 |
| Middle frontal gyrus | 3.54 | | -36 -2 46 | 219 |
| Inferior occipital gyrus | 3.74 | | -36 -74 -4 | 113 |
| Insula | 3.01 | | -38 6 8 | 29 |
| Cerebellum | 2.84 | | -6 -54 -40 | 29 |
| Posterior cingulate | 2.92 | | -24 -56 6 | 27 |
| Precuneus | 2.73 | | -24 -80 40 | 25 |
| Superior frontal gyrus | 2.61 | | -12 62 -12 | 22 |
| Cingulate gyrus | 2.70 | | -20 -16 38 | 12 |
| Precentral gyrus | 2.66 | | -32 -14 28 | 7 |
| Right hemisphere |  | |  |  |
| Insula | 8.78 | | 44 -18 0 | 5514 |
| Precuneus | 4.23 | | 6 -68 24 | 1133 |
| Inferior frontal gyrus | 3.40 | | 52 12 24 | 325 |
| Cingulate gyrus | 3.58 | | 20 -2 48 | 214 |
| Corpus callosum | 4.03 | | 8 -30 22 | 170 |
| Cerebellum | 2.70 | | 12 -50 -50 | 47 |
| Insula | 3.08 | | 28 18 8 | 39 |
| Middle frontal gyrus | 2.77 | | 54 0 42 | 23 |
| Posterior cingulate cortex | 2.61 | | 22 -56 6 | 17 |
| Caudate nucleus | 2.53 | | 12 24 6 | 7 |

Regions where activation was significant in response to all experimental stimuli (expected and unexpected sounds and silences) compared with fixation cross baseline at p<0.001 uncorrected. Peak t = test statistic at the voxel showing greatest activity in a cluster. MNI – Montreal Neurological Institute. Cluster = number of voxels activated at p < 0.01, uncorrected, in a cluster.

## 6.3. Results

The contrast of all experimental stimuli versus fixation cross baseline at p<0.01, uncorrected, revealed activation in several brain areas, including bilateral auditory cortex (Table 6.1).

Whole brain analysis

The contrast of all unexpected, versus expected auditory stimuli (silence, sound, low-and high-pitched tones, neutral and salient words) revealed significantly increased activation in the right, extending to the left lingual gyrus and left hippocampal gyrus in the whole brain analysis (Table 6.2, Figure 6.1).

VOI analysis

There were no significant activations in response to all unexpected, compared with all expected, stimuli within the VOI.

**Table 6.2. Areas activated by unexpected, compared with expected, stimuli from fMRI Sound/Silence, Pitch and Salience Experiments, combined.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Region (Brodmann area) | Peak *t* | FWE-*p* | MNI coordinates (*x y z*) | Cluster |
| R (extending to L) lingual gyrus (BA 19) | 5.75 | 0.002 | 14 -62 -10 | 2475 |
| L hippocampal gyrus (BA 36) | 4.89 | 0.05 | -22 -42 -14 | 156 |

Areas which showed increased activity in response to unexpected, compared with expected stimuli in the whole brain analysis at voxel-level threshold p<0.05 FWE (family wise error)-corrected. Peak t = test statistic at the voxel showing greatest activity in a cluster. Cluster – extent of the cluster at p<0.001, uncorrected. MNI- Montreal Neurological Institute. L- left, R –right.

**E:\phd\all exp unexp vs exp.TIFFigure 6.1. Areas activated significantly more by unexpected silence, sounds, low-and high-pitched sounds and neutral and salient words, versus those expected.** Activations in the lingual gyrus (red circles) and in the left hippocampal gyrus (orange circle) (Table 6.1) are mapped on the coronal, saggital and axial surface (from left to right) of a SPM glass brain image. Voxel threshold was p<0.05 FWE-corrected. SPM, statistical parametric mapping.

## 6.4. Discussion

This chapter presents the combined results of the three studies investigating neural activity in the auditory cortex in healthy volunteers in response to unexpected, compared with expected, auditory stimuli. The studies employed tasks where participants learned associations between visual cues (shapes) and auditory outcomes: sound and silence (fMRI Sound/Silence Experiment), low-and high-pitched sounds (fMRI Pitch Experiment) and neutral and salient words (fMRI Salience Experiment). Unexpected, compared with expected, auditory stimuli evoked significantly increased activity in the bilateral lingual gyrus (BA 19) and in the left hippocampal gyrus (BA 36). This finding is not in line with the hypothesis, which predicted that expectation would modulate activity in the auditory cortex.

Increased activity in the hippocampus in response to unexpected, compared with expected, stimuli, could be due to its role in detecting associative novelty (i.e. a familiar object in a new configuration, as opposed to stimulus novelty – occurrence of a new object) (Kumaran and Maguire, 2006). Such detection of change in the environment is thought to involve a comparison of an expectation derived from a retrieval of the representations stored in memory with current external stimuli. The hippocampus is uniquely suited for this operation due its role in associating and integrating unrelated elements of the environment and comparing these configurations with sensory input (Olsen et al., 2012). For instance, the hippocampus was found to activate in response to familiar visual objects shown in a new spatial position in relation to the background (Howard et al., 2011) or in a different sequence once the expectation was set by a cue (Kumaran and Maguire, 2006).

Activation in the bilateral lingual gyri in response to an unexpected auditory stimulus were also found in an oddball task with no visual cues (Schock et al., 2012). In that task, however, participants were watching faces whilst being presented with the auditory stimuli. The authors suggest that such increase in activity in the lingual gyri could result from a mechanism in which initiation of attention switch towards the acoustic change by neural networks in auditory cortex increases excitability of other sensory areas. Hence, it is plausible that in the current study processing of unexpected auditory stimuli increased excitability of visual cortex, leading to increased response to expectation breach.

The lingual gyri, next to the fusiform and the posterior cingulate gyri are part of the ventral visual stream involved in recognizing shapes and objects (Karnath et al., 2009). Since the task in this study employed geometrical shapes as cues, increased activity in the lingual gyri could be related to the processing of the cue which preceded presentation of the unexpected auditory stimulus. It could be that, once the auditory cortex processes the unexpected auditory event, it signals this breach of expectation to the visual cortex. This communication might serve updating of the validity of the cue. In the associative learning framework, such increased activity in the cue-specific brain area could reflect increased associative learning resulting from processing of unexpected outcome.

It is not clear why unexpected, compared with expected stimuli from the three experiments failed to activate auditory cortex. Increased activation in the lingual gyri and the left hippocampus in response to unexpected, compared with expected, auditory stimuli suggest that associations between the visual cues and auditory outcomes were learned. A significant response in the auditory cortex to unexpected, compared with expected, sounds was found in the Sound/Silence FMRI Experiment, where the acoustic difference between the auditory stimuli (sound versus silence) was relatively large. Therefore, a plausible explanation is that the acoustic difference between the low- and high-pitched tones and the neutral and salient words was insufficient to evoke a difference in the activity in the auditory cortex that could be detected with fMRI method. Future studies could employ similar paradigms varying the acoustic difference between the auditory stimuli in order to further elucidate the mechanisms of processing unexpected auditory outcomes in the auditory cortex.

Prediction –dependent activity in the cortex processing the cue found in the current study might be important in the maintenance of auditory hallucinations. Since low mood is often a precipitant of the ‘voices’ (Nayani and David), it could be the expectation of the ‘voices’ is an outcome cued by sadness, generated by the network of areas along the cortical midline, involved in self-referential processing (Farb et al., 2010). A prediction of threat could be generated by the MTG and projected to the auditory cortex. A reduction in prediction error produced in response to external input that does not match the expectation could mean that the cue-generating areas do not receive a signal informing about a discrepancy between the outcome (expectation) and external stimuli. Such failure in communication might mean that the validity of the cue (sadness) is not modified and the association between the mood and the ‘voices’ would be sustained. This mechanism could therefore contribute to the maintenance of auditory hallucinations.

# Chapter 7.

# General discussion

## 7.1. Contributions of the current work to the existing knowledge

### 7.1.1. Normal auditory predictive coding

The aim of the project described in this thesis was to explain the mechanisms of auditory predictive coding in healthy participants and arrive at a model of the auditory processing that would improve the understanding of the mechanism of auditory hallucinations. The additional goal of the current work was to formulate a theoretical model of the ‘voices’. The specific aims of the studies were to elucidate i) how auditory expectation affect reaction time and accuracy, ii) how auditory expectation modulates neural activity in the auditory cortex and iii) whether the effects of the auditory prediction on neural activity depend on the salience of the auditory stimuli**.**

Chapter 1 contains the synthesised research findings in the area of predictive coding in perception (Rao and Ballard, 1999), specifically in generation of prediction and prediction error in auditory perception. Evidence suggests that such expectations could be generated in the prefrontal cortex (Leaver et al., 2009, McIntosh et al., 1998) and transmitted to the auditory cortex. Communicating a prediction might involve a synchronization of the firing of neurons in these two areas (Fries, 2005, Ghuman et al., 2008). The auditory cortex would then compare the prediction with the actual input and in case of a discrepancy, form a prediction error signal. Prediction error has been found to be associated with increased neural activity relative to processing an expected outcome (Fletcher et al., 2001, den Ouden et al., 2009). Such increase in activity could be underpinned by the formation of the new neural circuits, driven by NMDA receptors to glutamate (Strelnikov, 2007). The prediction error would then be signalled to the PFC (Opitz et al., 2002).

The remaining chapters aimed to test the model of healthy predictive coding. With this aim, the Behavioural Sound/Silence and Pitch Experiments described in Chapter 3 employed associative learning tasks consisting of visual shapes serving as cues for auditory stimuli and investigated the relationship between auditory prediction and reaction time. Results revealed that a breach of expectation was associated with trend-level increase in reaction time to unexpected, compared with expected, sound and silence, a trend-level decrease in accuracy in responding to unexpected, versus expected, silence (when sound was predicted), and a trend-level increase in accuracy in responding to unexpected, relative to expected, sounds (when silence was predicted). The response time to sounds of unexpected, compared with expected, pitch, was similar. Participants were significantly more accurate in responding to unexpected, compared with expected, low-pitched tones. These results suggest that the effects of expectation on behaviour depend on the configurations and sufficient acoustic differences between the auditory stimuli employed. Specifically, sound can be a salient stimulus when contrasted with silence. Therefore, when participant expected silence and instead were presented with a sound, the presented stimulus might have startled them and thus reduced the potential increase in response latency associated with its unexpectedness. Similarly, when participants expected a sound, they could have responded to the predicted event before they realized that no stimulus was presented (unexpected silence). Such interaction between the employed stimuli should be carefully considered in future studies investigating auditory predictive coding.

Functional MRI Sound/Silence and Pitch Experiments, described in Chapter 4, aimed to elucidate the neural correlates of auditory expectation in the auditory cortex in the context of unexpected event (when none or a different outcome is expected) and unexpected omission (when an event is expected). Results of the associative task consisting of visual shapes predicting sounds or silence revealed significant prediction dependent responses in the network of brain areas consisting of the left middle and superior temporal gyri, left insula, left middle frontal gyrus and right STG. Functional MRI Salience Experiment, presented in Chapter 5, employed a visual-auditory associative task where auditory outcomes differed in emotional salience. The results revealed a potential involvement of the right posterior cingulate gyrus in processing of a breach of salient expectation, and modulation of auditory cortex by ACC during presentation of emotionally salient stimuli. The results of these three studies indicate that the model of the normal auditory predictive coding presented in Chapter 1 might need to be modified.

The combined results of FMRI Sound/Silence, Pitch and Salience Experiments, described in Chapter 6, show that when a visual cue evokes an auditory prediction, unexpected auditory outcomes activate the hippocampus. Such increased activity suggests that the associations between the stimuli are stored in memory. The hippocampus might be involved in retrieving the stored representation of the outcome induced by the cue and in comparing the expectation with the external input and thus detecting change in the environment (Kumaran and Maguire, 2006).

The results of the studies do not provide evidence of the role of PFC in processing auditory prediction error. Increased activity of the frontal cortices in response to a prediction error was found in some (Mitchell et al., 2005, Opitz et al., 2002), although not all (Opitz et al., 2005) MMN studies. The increase in activity in the left middle frontal gyrus approached significance in response to unexpected, compared with expected, high-pitched tones. It is plausible, that lack of significant and pronounced increase in activity in PFC in response to unexpected auditory outcomes is due to methodological aspects of the study. For example, it could be that prediction-error related increase in PFC activity occurs mainly when participants are aware of the unexpected stimulus (Mitchell et al., 2005, McIntosh et al., 1999). However, an alternative explanation for lack of response in prefrontal cortex to unexpected sounds and silences could be that the frontal cortex does not play as important a role in forming and updating auditory prediction as the model presented in Chapter 1 predicted.

The results of the fMRI Sound/Silence study revealed that whilst the left MTG responded to both unexpected silences and sounds, STG showed significantly increased response only to unexpected sounds. This difference in the responses to unexpected, compared with expected, silence between these areas of the auditory cortex suggests a predictive coding hierarchy in the auditory cortex. Evidence shows that MTG is involved in the processing of relatively abstract (e.g. speech) and ambiguous auditory stimuli (Davis and Johnsrude, 2003, Kilian-Hutten et al., 2011). Therefore, this area could be higher in the cognitive hierarchy than STG and thus generate the auditory prediction and convey it to STG. The auditory prediction in MTG is represented in a relatively abstract form. Hence even if no stimulus is expected, the prediction of no input is associated increased activity in relation to baseline (E0, Figure 4.4a). The STG, on the other hand, represents the expectation in a more stimulus-specific manner. Therefore, when the actual external stimulus is a sound (S1, Figure 4.4a), activity increases. However, if a sound is predicted (E1, Figure 4.4b) and the presented auditory event is unexpected silence (S0, Figure 4.4b), the silence is associated with low level of activity compared with sound despite its unexpectedness. We propose that the MTG then assigns a meaning to the STG response to the external stimulus in the context of the expectation, i.e. unexpected silence (S0, Figure 4.4b) is represented by higher response than expected silence.

Since the left insula also responded to unexpected sound, but not unexpected silence, its place in the auditory predictive coding hierarchy could be similar to that of STG. Results of the fMRI Pitch Experiment suggest that the process of updating auditory prediction in response to an error signal could involve increased connectivity between the bilateral auditory cortices.

The results of the fMRI Salience Experiment show that the increase in activity in the right posterior cingulate gyrus approached significance in response to unexpected neutral words (when a salient word was expected) compared with its expected counterpart. This area could, therefore, be part of the network processing auditory prediction error. Such increased activation in response to an unexpected neutral stimulus could be underpinning the inhibition of a response prepared to the expected salient stimulus, as suggested by evidence showing a role for the posterior cingulate gyrus in the top-down, effortful inhibition (Ciesielski et al., 2011).

The combined results of FMRI Sound/Silence, Pitch and Salience Experiments, show that when a visual cue evokes an auditory prediction, unexpected auditory outcomes activate the area that processes the cue (bilateral lingual gyri). These results suggest that a breach of auditory expectation that had been induced by a visual cue could be signalled to the visual cortex, possibly in order to update the perceived validity of the cue.

Hence, it appears that the process of auditory predictive coding is more complex and involves greater number of areas than it was initially thought. The process is likely to include interactions between the perceptual areas that process the cue and those that respond to outcome, as well as memory centres and areas that might be involved in inhibiting the response when the external stimulus is less emotionally salient that the expected outcome.

### 7.1.2. Auditory predictive coding and auditory hallucinations

Chapter 1 reviewed the main current models of auditory hallucinations: reality discrimination (Bentall, 1990), source memory and inhibition (Waters et al., 2006), inner speech/self-monitoring (Stephan et al., 2009) and auditory perceptual model (Hunter and Woodruff, 2004). Whilst each of the models explains some aspects of the ‘voices’, none of them provides a full explanation of the detailed mechanisms and phenomenology of the hallucinations. In order to close this gap we formulated a new hypothesis of the mechanisms underlying the ‘voices’ (expectation-perception model). The model proposes that auditory hallucinations arise from abnormalities in the auditory predictive coding, specifically, from the absence or attenuation of prediction error. As a result the predictions of the auditory input are insufficiently constrained by prediction error and misinterpreted as an auditory signal evoked by external stimulation.

We proposed specific mechanisms underlying the abnormalities in processing prediction error: 1) aberrant modulation of thalamus by prefrontal cortex, 2) absence or impaired transmission of external input, 3) neurotransmitter dysfunction and abnormal connectivity, 4) hyperactivity in auditory cortex and broad prior probability. Evidence supporting these mechanisms includes functional and structural abnormalities in the OFC (Homayoun and Moghaddam, 2008, Silbersweig et al., 1995), in the bottom-up connections between the thalamus and PFC (Lewis and Sweet, 2009), in the feedforwad pathways within the auditory cortex (Sweet et al., 2004, Sweet et al., 2007), as well as abnormal neurotransmitter function and brain connectivity in schizophrenia (Coyle, 2006, Skudlarski et al., 2010).

The results of the experimental work presented in this thesis did not provide evidence of the involvement of PFC in the predictive coding. Hence, the role of abnormal modulation of thalamus by the frontal areas in the auditory hallucinations remains to be established. The results of the work presented in this thesis suggest that auditory expectation could be formed in the MTG and sent to STG. It has been shown that MTG is involved in abstract cognitive functions such as extracting meaning from ambiguous signal (Kilian-Hutten et al., 2011). The findings of FMRI Pitch Experiment indicate that bilateral MTG responds significantly more to low-, versus high-pitched tones. Pitch is one of the cues in recognizing emotional prosody (Leitman et al., 2005) and MTG has been shown to respond to affective cues in speech (Mitchell et al., 2003). Therefore, since hallucinatory percepts are often threatening in content and spoken in a male (i.e. relatively low-pitched) voice, MTG could be involved in generating the prosody and gender of the ‘voices’. Hence, it is plausible that MTG forms the auditory expectation of a threatening verbal message often spoken in a male voice and sends this prediction to STG.

Results of the FMRI Salience Experiment also show that activity in the auditory cortex was modulated by the left anterior cingulate gyrus during processing of salient, compared with neutral, stimuli. Activity in this area has been shown to be associated with auditory hallucinations (Lahti et al., 2006, Szechtman et al., 1998), to correlate with activity in the auditory cortex and with auditory attention in those prone to hearing ‘voices’ (Cleghorn et al., 1990, Lewis-Hanna et al., 2011). Since the content of the auditory hallucinations is often salient (Nayani and David, 1996), increased activity in the anterior cingulate could contribute to the generation of these false percepts through imbuing activity in the auditory cortex with emotionally-salient signal.

The neural networks representing expectation in the STG could overlap with those that are excessively spontaneously active (E1/S2, see Figure 4.8a, b). Hence, in line with the saturation hypothesis (Woodruff et al., 2007), neural resources that are available for processing the external stimulus will be limited and the response of the auditory cortex to them diminished. Therefore, the physiological spontaneous activity (Hunter et al., 2006) when exaggerated, can contribute to the reduction in the prediction error signal (PE3=E1/S2-S3, Figure 4.8a, PE0=E1/S2-S0, Figure 4.8b). The hyperactivity might also contribute to a misinterpretation of the bottom-up signal sent by STG to MTG as that corresponding to a sound (S2, Figure 4.8b) when it is in fact a response to silence (S0, Figure 4.8b). The failure in generating a correct prediction error signal could lead to MTG incorrectly construing the bottom-up signal as consistent with the expectation and a perception of the prediction as a real, external signal, resulting in auditory hallucinations.

The results of the effective connectivity suggest that a breach of auditory expectation is associated with modulation of auditory areas that are higher in the hierarchy (associative auditory cortex) by those that are lower in the hierarchy (primary auditory cortex). Thus, abnormal connectivity found in schizophrenia, both anatomical (Sweet et al., 2004) and functional (Skudlarski et al., 2011) could contribute to auditory hallucinations through aberrant modulation of the activity in the auditory cortex in response to a breach of expectation.

The results of the current work suggest that a breach of expectation in healthy individuals is processed not only by the brain area responding to the unexpected stimulus, but also that involved in processing the cue which stimulated the retrieval of the prediction. Both abnormal connectivity and the impairment in prediction error generation could lead to a failure in communicating the breach of expectation to the cue-processing areas. In auditory hallucinations one of the cues for the hallucinatory expectation could be mood (Nayani and David, 1996). Hence, the cue-processing areas could include limbic system or areas along the midline, involved in self-referential processes (Farb et al., 2010). The resulting inability to update the validity of the cue could contribute to the maintenance of auditory hallucinations. Finally, the findings of the work described in this thesis indicate that activity in the left hippocampal gyrus underpins updating the associations in response to prediction error. It has been shown that the left hippocampus has decreased volume (Herold et al., 2012) and reduced connectivity with STG in schizophrenia (Sommer et al., 2012). These abnormalities could lead to a situation where the left hippocampus is unable to retrieve the appropriate outcome stored in memory and to effectively communicate it to the STG.

Therefore, abnormalities involved in generation and maintenance of auditory hallucinations could involve mechanisms such as abnormalities in bottom-up pathways within the auditory cortex (Sweet et al., 2003), neurotransmitter function and abnormal connectivity (Friston, 1998; Skudlarski et al., 2010), in particular between bilateral auditory cortices, bottom-up connectivity within the auditory system, and between auditory cortex and ACC. Hyperactivity in the auditory system (Lewis-Hanna et al., 2011) and broad prior probability might also contribute to auditory hallucinations. The MTG might be involved in generating the auditory expectation, including the prosody and gender of the voices (Birkett et al., 2007; Sokhi et al., 2005).

## 6.2. Limitations

A potential limitation of all the studies described in this thesis is the lack of a measure of participants’ awareness of the associations. Such measure could help to establish whether the effects of expectation on reaction time or neural activity depend on the awareness of the associations. However, it has been shown that both MMN and expectation-dependent increase in neural activity occur even when participants are not aware of the contingencies (Opitz et al., 2005, den Ouden et al., 2009). Since the tasks employed in this work required high level of concentration and participants were not informed of the contingencies it is likely that they were not aware of them.

The small number of unexpected, compared with expected, trials could have limited the power of statistical analysis in the behavioural and fMRI studies and therefore reduce the likelihood of detecting some of the effects. Similarly, the number of participants in the fMRI studies (Sound/Silence, Pitch and Salience) might have been insufficient to detect effects of expectation. Due to the difference in the number of trials in ‘expected’ and ‘unexpected’ conditions it was not practical to compare activations evoked by ‘expected’ compared with ‘unexpected’ stimuli, since any difference could have been attributed to greater power in the ‘expected’ condition. Nevertheless, such imbalance was necessary in order to maintain the ‘unexpected’ nature of some of the stimuli. Finally, lack of activation in auditory cortex in response to less probable auditory outcomes in the FMRI Pitch and Salience Experiments could partly be due to the increased baseline activity evoked by the noise of the fMRI scanner and partly to insufficient acoustic difference between the auditory stimuli. The effects of such noise can be greatly reduced by the sparse-sampling scanning method, employed in this study, however the noise cannot be eliminated completely. This conclusion was derived from the fact that activity in the auditory cortex was modulated by expectation only in FMRI Sound/Silence Experiment, where the acoustic difference between the auditory events was relatively large (a sound versus silence).

## 6.3. Future research

Future studies could employ associative learning tasks in order to investigate the auditory predictive coding in both healthy volunteers and those experiencing auditory hallucinations. Behavioural studies could employ greater number of trials, while preserving the ratio of the expected versus unexpected stimuli. Such increase in the number of trials would increase the power of the statistical analysis and the likelihood of detecting effects of expectation. It could also be beneficial to change the pitch of the sounds employed so that the difference between them is more obvious. Other designs could employ differences in duration or loudness of the stimuli. A measure of awareness of the associations would be useful in establishing the relationship between potential effects of expectation and conscious prediction.

Neuroimaging studies employing associative learning to investigate effects of perceptual prediction would benefit from greater number of trials and participants. As in behavioural studies, a questionnaire measuring participants’ awareness of the contingencies would be helpful in establishing whether learning of associations took place and how it affected neural activity. With larger sample the scores of questionnaires measuring the tendency to hallucinating could be correlated with neural activity in order to probe the effects of potential hallucinations on neural processing of prediction error. Greater contrast between the auditory stimuli could increase the chance of finding a difference in auditory cortex activity. Salient stimuli could include non-verbal sounds with emotional meaning. Healthy individuals who hear ‘voices’ should be recruited in order to differentiate between abnormalities in neural activity related to schizophrenia and those specifically related to auditory hallucinations.

## 6.4. Final Conclusion

At the outset of this work we proposed a new model of auditory hallucinations, which describes the mechanisms underpinning the generation of the ‘voices’. Since a crucial concept in the expectation-perception model is the auditory predictive coding, we conducted a series of experiments investigating behavioural and neural correlates of auditory expectation. Our results indicate a wide network of brain areas involved in processing auditory prediction error. Left middle temporal gyrus responded to unexpected sounds and silences, whilst left superior temporal gyrus activated significantly only to unexpected sounds. Such difference in activity suggests a hierarchy in processing expectation and prediction error such that middle temporal gyrus performs relatively abstract processing, i.e. generates expectation and interprets activity of superior temporal gyrus. Responses of the latter are more stimulus-constricted, i.e. it responds with greater activity to the sound and very little activity to silence, whether expected or unexpected. The middle and superior temporal gyri been shown to have abnormal structure and function in individuals suffering from auditory hallucinations. Such correspondence between the function in prediction error processing and abnormality in auditory hallucinations might indicate that aberrations in processing prediction error could contribute to perception of ‘voices’. The results also revealed that bilateral visual cortex involved in recognizing shapes responds with increased activity to unexpected, compared with expected auditory stimuli. This finding suggests that in perception of associated stimuli the brain area processing the cue updates the validity of the signal in response to the activity in the brain area processing the outcome. Increased activity in the left hippocampal gyrus might indicate the process of updating the associations between the stimuli in memory. We were able to devise a model of normal (healthy) auditory predictive coding and a hypothetical model of auditory predictive coding in auditory hallucinations. Such model will allow future comparison of the processing of unexpected auditory outcomes between healthy individuals and those suffering from auditory hallucinations. It might thus be possible to test the predictions of the expectation-perception hypothesis and to improve the understanding of auditory hallucinations.

**Publications during PhD**

**Published**

Nazimek, J.M., Hunter, M.D., Woodruff, P.W. (2012) Auditory hallucinations: expectation-perception model. *Medical Hypotheses,*78, 802-810.

**In submission**

Nazimek, J.M., Hunter, M.D., Hoskin, R.J., Wilkinson, I., Woodruff, P.W. Neural basis of auditory expectation within the temporal cortex.

**Abbreviations**

AC – auditory cortex

ACC – anterior cingulate cortex

BA – Brodmann Area

BOLD – blood oxygenation level dependent

CG – cingulate gyrus

CR – conditioned response

CS – conditioned stimulus

CSF – cerebrospinal fluid

DCM – dynamic causal modeling

E - expectation

EPI- echo planar imaging

fMRI – functional magnetic resonance imaging

FWHM – full width half maximum

L- left

LSHS – Launay-Slade Hallucinations Scale

MNI – Montreal Neurological Institute

MTG – middle temporal gyrus

NART – National Adult Reading Test

OFC – orbitofrontal cortex

PE – prediction error

PFC – prefrontal cortex

PPI- Psychophysiological interactions

R – right

S – signal

SD – standard deviation

SEM – structural equation modeling

STG – superior temporal gyrus

SPM – statistical parametric mapping

TE – echo time

TR – repetition time

TRN – thalamic reticular nucleus

TTG – transverse temporal gyrus

US – unconditioned stimulus

UR – unconditioned response

VOI- volume of interest

WAIS-R – Wechsler Adult Intelligence Scale – revised

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