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Research report

# Mismatch negativity (MMN) reveals inefficient auditory ventral stream function in chronic auditory comprehension impairments

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ABSTRACT

*Background:* Auditory discrimination is significantly impaired in Wernicke's aphasia (WA) and thought to be causatively related to the language comprehension impairment which characterises the condition. This study used mismatch negativity (MMN) to investigate the neural responses corresponding to successful and impaired auditory discrimination in WA.

*Methods:* Behavioural auditory discrimination thresholds of consonant-vowel-consonant (CVC) syllables and pure tones (PTs) were measured in WA ($n = 7$) and control ($n = 7$) participants. Threshold results were used to develop multiple deviant MMN oddball paradigms containing deviants which were either perceptibly or non-perceptibly different from the standard stimuli. MMN analysis investigated differences associated with group, condition and perceptibility as well as the relationship between MMN responses and comprehension (within which behavioural auditory discrimination profiles were examined).

*Results:* MMN waveforms were observable to both perceptible and non-perceptible auditory changes. Perceptibility was only distinguished by MMN amplitude in the PT condition. The WA group could be distinguished from controls by an increase in MMN response latency to CVC stimuli change. Correlation analyses displayed a relationship between behavioural CVC discrimination and MMN amplitude in the control group, where greater amplitude corresponded to better discrimination. The WA group displayed the inverse effect; both discrimination accuracy and auditory comprehension scores were reduced with increased MMN amplitude. In the WA group, a further correlation was observed between the lateralisation of MMN response and CVC discrimination accuracy; the greater the bilateral involvement the better the discrimination accuracy.

*Conclusions:* The results from this study provide further evidence for the nature of auditory comprehension impairment in WA and indicate that the auditory discrimination deficit is grounded in a reduced ability to engage in efficient hierarchical processing and the construction of invariant auditory objects. Correlation results suggest that people with chronic

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WA may rely on an inefficient, noisy right hemisphere auditory stream when attempting to process speech stimuli.

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## 1. Introduction

Auditory language comprehension impairments post stroke have been associated with multiple cognitive sources; most classically a perceptual impairment disrupting the analysis of the acoustic structure of words (Eggert, 1977; Wernicke, 1874). Although perceptual impairments that disrupt comprehension are severe, they are not absolute, in that most types of acoustic change can be perceived when sufficient acoustic difference between stimuli is provided (Robson, Keidel, Lambon Ralph, & Sage, 2012; Robson, Sage, & Lambon Ralph, 2012). Using the mismatch negativity (MMN) event-related potential (ERP), this study investigated neural responses to verbal and non-verbal auditory changes that were either perceptible or non-perceptible to individuals with Wernicke's Aphasia (WA). Further analyses investigated the relationship between ERP morphology and neuropsychological profile.

There are two main post-stroke syndromes involving comprehension impairments that are wholly or partially attributed to disrupted auditory-perceptual processing: word deafness and WA. Word deafness is considered a 'pure' form of perceptually-based comprehension impairment, which involves a selective impairment of the capacity to analyse the acoustic structure of speech. People with word deafness have often resolved from WA (Saffran, 2000), a more complex syndrome of impairments but which also involves deficits in language comprehension. The language comprehension impairment of WA has a significant auditory-perceptual component but is also compounded by further disruption to semantic, phonological and executive processing (Robson, Keidel, et al., 2012; Robson, Sage, et al., 2012). This study focuses only on the auditory-perceptual element of WA.

Individuals with WA have lesions which can affect large regions of the middle cerebral artery territory of the left hemisphere. Lesions most consistently affect the mid-to-posterior superior and middle temporal gyri, including the primary auditory cortex, and the inferior parietal lobe; however, further extension into the anterior temporal lobe and pre-frontal region is not uncommon (Bogen & Bogen, 1976; Dronkers, Redfern, & Ludy, 1995; Robson, Sage, et al., 2012). This lesion distribution overlaps with the ventral auditory pathway; a processing stream specialised for auditory pattern recognition (DeWitt & Rauschecker, 2012; Lomber & Malhotra, 2008). The ventral pathway is thought to originate (in humans) in mid-Heschl's gyrus and project laterally, traversing the planum temporale and, anteriorly, along the superior temporal gyrus/sulcus (STG/S) into the inferior frontal lobe (DeWitt & Rauschecker, 2012; Rauschecker & Scott, 2009). The ventral streams are hierarchal processing networks which allow for the identification and abstraction of auditory objects through combining and integrating low-level feature information into invariant higher-order forms (Griffiths & Warren, 2004; Scott, 2005). The early stages of the ventral stream, such as the auditory core, contain neuronal populations which are tuned to specific physical features (Bitterman, Mukamel, Malach, Fried, & Nelken, 2008) with downstream neuron populations displaying greater sensitivity to patterns, i.e., are less influenced by physical variation (Sadagopan & Wang, 2009). In the left hemisphere, neuron populations are responsive to phonetic speech features. The mid-STG displays properties of invariant phoneme recognition and the left anterior STG/S responds to invariant word-forms (Chang et al., 2010; Davis & Johnsrude, 2003; Marinkovic et al., 2003; Scott, Rosen, Lang, & Wise, 2006).

The lesion pattern in WA overlaps with both early (feature-specific) and, in some cases, late (invariant-pattern) regions of the left auditory ventral stream, a distribution which implies impairments in the primary analysis of decomposed auditory inputs and in the re-construction of auditory inputs into abstracted word-forms. This neurobiological model and lesion profile tally with behavioural findings in WA. Auditory-perceptual impairments are measured, clinically and in research, as an individual's capacity to detect acoustic changes in words or pseudowords (e.g.,/poth/vs/koth/) or non-linguistic stimuli (e.g., difference between frequency sweeps). Phonological discrimination is highly impaired in WA (Baker, Blumstein, & Goodglass, 1981; Blumstein, Baker, & Goodglass, 1977) as is the detection/discrimination of non-verbal stimuli containing rapid temporal modulations (Fink, Churan, & Wittmann, 2006; Robson, Grube, Lambon Ralph, Griffiths, & Sage, 2013). In contrast, auditory judgments which require processing of static spectral information, such as pure tone (PT) discrimination, remain largely intact in individuals with left hemisphere lesions (Robin, Tranel, & Damasio, 1990). The capacity to detect speech-relevant spectro-temporal modulations and the capacity to discriminate speech sounds is statistically related to the degree of comprehension impairment in WA (Robson et al., 2013; Robson, Sage, et al., 2012). However, in these cases, auditory discrimination/detection is not absent; discrimination can be achieved using stimuli with sufficient acoustic differences. For example, individuals with WA can discriminate/fid/and/gid/but not/kol/and/pol/ (Robson, Keidel, et al., 2012). Given that these stimuli are of the same nature, it is unlikely that they would engage different neural processing networks in neurologically normal individuals. Therefore, understanding the neural patterns which correspond to this behavioural "accuracy" and "inaccuracy" may provide insights into the functioning/adaptation of the ventral stream and change detection networks in response to damage. Furthermore, investigating such mechanisms is of clear clinical importance. Behavioural therapy for WA often attempts to ameliorate the phonological processing deficit, i.e., to make non-

discriminable changes perceptible. Understanding the neural response corresponding to behavioural success and how these neural responses are linked to the wider neuropsychological profile may help to establish therapeutic approaches that are neurobiologically sound and may provide a framework from which to evaluate neural changes that underpin therapy-induced behavioural change.

ERPs are a non-invasive measure of cortical function that have been successfully employed in the investigation of central auditory processing in a range of clinical populations (Naatanen & Escera, 2000). The MMN auditory ERP component is sensitive to auditory change detection and is elicited by infrequent deviant stimuli embedded in a sequence of repeating standard stimuli (auditory oddball paradigm: Naatanen, Paavilainen, Rinne, & Alho, 2007). The MMN is a negative deflection with a fronto-central scalp distribution, peaking between 150 and 200 msec post stimulus onset (Naatanen et al., 2007). This fronto-central distribution reflects cortical sources in the ventral stream in the bilateral auditory cortices (the exact cortical generators are stimulus dependent) (Naatanen et al., 2007) plus further frontal generators with a right hemisphere asymmetry (Deouell, Bentin, & Giard, 1998). The frontal generators have been associated with involuntary attention switching and the auditory cortices sources associated with acoustic features change detection (Deouell et al., 1998). Network analysis, using measures of phase coherence/synchronisation, have confirmed that functional integration of these source regions is induced by deviant stimuli. For example, increased theta and alpha band coherence has been observed between ipsilateral temporal-frontal regions and temporal-parietal regions following presentation of deviant stimuli (Hsiao, Cheng, Liao, & Lin, 2010) while increased gamma band coherence has been identified over short range connections within temporal regions and long range inter-hemispheric connections between the temporal lobes (Nicol et al., 2012).

MMN is a popular measure for use with clinical populations as it does not require active attention to the stimuli and can, therefore, be elicited passively. Using multiple deviant auditory oddball paradigms, this study measured MMN responses in WA and control participants to PT and consonant-vowel-consonant (CVC) non-word syllable deviants that could and could not be reliably discriminated. PTs were selected for their relatively preserved processing in WA. This enabled a baseline comparison of neural responses corresponding to similar behavioural patterns in WA and control participants. Conversely, CVC processing is impaired in WA, enabling the investigation of neural responses to perceptible and non-perceptible changes that were all within the perceptible range in control participants. Control participants were additionally exposed to perceptible and non-perceptible CVC changes; non-perceptible CVC deviants were within phonological category changes. MMN morphology (amplitude and latency) was analysed and compared between group and perceptibility conditions. Within the WA group, further analyses examined the relationship between neuropsychological profile (discrimination and comprehension) and MMN morphology for the different levels of perceptibility. Given the clinical focus on improving auditory discrimination in these cases, this study was particularly interested in investigating the presence and nature of the neural responses to non-perceptible changes. In particular, this study aimed to distinguish between two potential sources of impairment: (1) phonological-auditory discrimination is impaired because acoustic differences are not identified at the most fundamental levels; i.e., no auditory change is processed; (2) Inability to discriminate speech sounds arises from inefficiencies in hierarchical processing; i.e., fundamental differences are detected but poorly reconstructed into abstracted word-forms. The first hypothesis predicts that no MMN will be observable to non-perceptible changes whereas the second hypothesis predicts detectable, but morphologically altered MMN to non-perceptible changes.

## 2. Methods

### 2.1. *Overview*

Behavioural discrimination thresholds of PTs and CVC syllable stimuli were measured in WA and control participants. The threshold results were then used to develop PT and CVC multiple deviant auditory oddball MMN paradigms. Two types of oddball were used in each condition; one oddball stimulus above the behavioural discrimination threshold (perceptible change from standard stimuli, "deviant-above") and one oddball below the behavioural discrimination threshold (non-perceptible change from standard stimuli, "deviant-below"). In the PT condition, the WA and control participants had the same standard, deviant-above and deviant-below. In the CVC condition, the control participants' deviant-above corresponded to the WA participants' deviant-below.

### 2.2. *Participants*

Seven individuals with WA (all male, mean age 70.6 yrs, SD 3.9, range 67–77) were recruited from community services in the North West of England. Seven age and hearing matched controls were subsequently recruited (two female, mean age 69.6 yrs, SD 6.1, range 60–77) and did not significantly differ from the WA participants on these variables and were within normal limits on the Addenbrooke's Cognitive Examination-Revised (Mioshi, Dawson, Mitchell, Arnold, & Hodges, 2006) (Table 1). All participants provided informed written consent. A favourable ethical opinion was granted for this study by the University of Manchester Research Ethics Committee.

#### 2.2.1. *WA background assessment and lesion profile*

All stroke participants had suffered from an infarction and were in the chronic stage of their recovery (mean number of months post onset 30.4, SD 11.6, range 20–54, Table 1). Diagnosis of WA was confirmed using the Boston Diagnostic Aphasia Examination – Short Form (Goodglass, Kaplan, & Barresi, 2001) (BDAE: Table 1). MRI T1-weighted scans were available for six of the seven WA participants. Images were acquired on a 3T Philips Achieva scanner with an eight-element SENSE head coil with a sense factor of 2.5. An inversion recovery sequence produced a 256 × 256 matrix of 128 transverse slices with 1 $mm^3$ voxels. Lesions were analysed using the automated lesion detection algorithm (Seghier,

**Table 1 – Background demographic and assessment data.**

| | Pt | Age | M.P.O | Ave. Hearing Thresh. | | Background assessments | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | L ear (dB SPL) | R ear (dB SPL) | BDAE fluency (%) | BDAE repetition (%) | BDAE comprehension (%) | ACE-R (max. 100) | MMSE (max. 30) |
| WA | DR | 77 | 20 | 38.8 | 38.75 | 47 | <1 | 2 | n/a | n/a |
| | DM | 68 | 25 | 18.8 | 21.25 | 47 | <1 | 3 | n/a | n/a |
| | DL | 74 | 23 | 17.5 | 20 | 63 | <1 | 5 | n/a | n/a |
| | EL | 69 | 34 | 40 | 38.75 | 75 | 10 | 14 | n/a | n/a |
| | LS | 67 | 24 | 46.3 | 55 | 70 | 22.5 | 18 | n/a | n/a |
| | MR | 67 | 33 | 47.5 | 18.75 | 68 | 22.5 | 20 | n/a | n/a |
| | CW | 72 | 54 | 56.3 | 47.5 | 100 | 22.5 | 42 | n/a | n/a |
| | Mean | 70.6 | 30.4 | 37.9 | 34.3 | 67.1 | 19.4 | 14.9 | | |
| | SD. | 3.9 | 11.6 | 14.6 | 14.5 | 18.1 | 11.3 | 14.0 | | |
| Control | DW | 73 | n/a | 25 | 27.5 | n/a | n/a | n/a | 92 | 30 |
| | DO | 70 | n/a | 41.25 | 35 | n/a | n/a | n/a | 98 | 28 |
| | RM | 73 | n/a | 28.75 | 31.25 | n/a | n/a | n/a | 95 | 30 |
| | CR | 69 | n/a | 37.5 | 23.75 | n/a | n/a | n/a | 99 | 30 |
| | BR | 77 | n/a | 30 | 47.5 | n/a | n/a | n/a | 78[a] | 26 |
| | PL | 61 | n/a | 26.4 | 29.6 | n/a | n/a | n/a | 9 | 29 |
| | PT | 60 | n/a | 13.75 | 6.25 | n/a | n/a | n/a | 97 | 30 |
| | Mean | 69.6 | | 28.4 | 27.1 | | | | 93 | 29 |
| | SD. | 6.1 | | 9.2 | 13.0 | | | | 7.12 | 1.5 |
| *t*-test | *t* score | | | 1.45 | .97 | | | | | |
| | *p* value | | | ns | ns | | | | | |

M.P.O. = months post stroke onset; BDAE = Boston Diagnostic Aphasia Examination – Short Form (Goodglass et al., 2001), ACE-R = Addenbrooke's Cognitive Examination – Revised (Mioshi et al., 2006), MMSE = Mini Mental State Examination (Folstein, Folstein, & McHugh, 1975). Average hearing threshold calculated as the average of pure tone thresholds at 500 Hz, 1 kHz, 2 kHz and 4 kHz.

[a] Low literacy level, otherwise within normal limits.

Ramlackhansingh, Crinion, Leff, & Price, 2008). The lesion overlap map (Fig. 1) displayed a distributed profile at the group level. Inspection of individual MRI/CT scans indicated that 5/7 stroke participants had lesions affecting the mid-anterior STG (within 1 $mm^3$ of MNI coordinates – 54 – 11 9) and posterior temporal gyrus (within 1 $mm^3$ of MNI coordinates – 65 – 29 11). The remaining two stroke participants (EL and DR) had lesions affecting the mid-to-posterior superior temporal sulcus/gyrus. Therefore, all stroke participants showed lesion affecting the left auditory ventral stream plus further involvement of regions in the left middle temporal cortex, inferior parietal lobe and prefrontal cortex.

### 2.3. *Behavioural and electroencephalography (EEG) data collection*

Behavioural and EEG data collection were carried out on separate occasions. The PT stimuli for this study were generated in Matlab and the CVC stimuli were recorded in a quiet environment and further manipulated, as described below, using Praat (www.praat.org). MMN stimuli were derived from behavioural thresholds which were estimated using adaptive-tracking procedures to establish the minimum perceptual difference between PTs (measured in semitones) and CVC syllables (based on phoneme confusability) for reliable discrimination. These threshold estimation methods are described extensively elsewhere (PT procedure in Robson et al., 2013; CVC discrimination used a modified version of the procedure in Robson, Keidel, et al., 2012). Briefly, participants heard three stimuli and were required to select which of three stimuli was the odd-one-out. The target never appeared in the central position, which acted as a reference stimulus. The perceptual difference between the target and reference stimuli was adaptively varied so that it decreased following consecutive correct responses and increased following one incorrect response (a reversal). PT thresholds were estimated over 50 trials, calculated as the mean

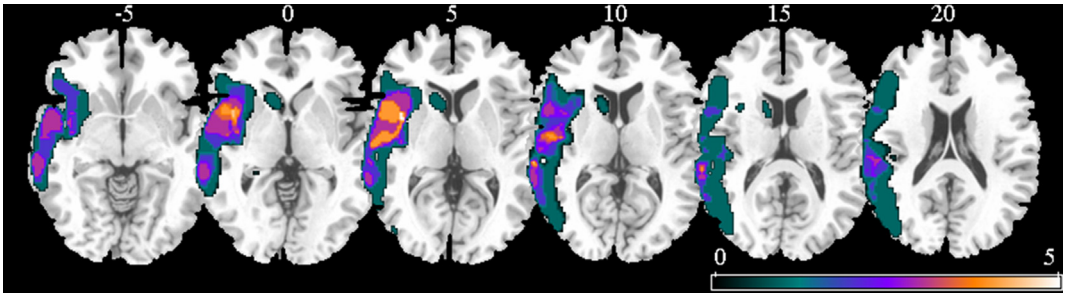


**Fig. 1 – Wernicke's Aphasia Lesion Overlap Map. Axial slices with corresponding MNI Z coordinate. Colour bar indicates number of WA participants with lesion in each voxel.**

of the final six reversals. CVC threshold estimation finished after eight incorrect responses; the threshold was calculated as the mean of the final four reversals.

#### 2.3.1. Behavioural stimuli parameters

(1) *PTs:* Each stimulus was 150 msec, separated by a 750 msec ISI, making a total trial length of 1.95 sec. The threshold procedure established the minimum frequency difference required for PTs to be discriminated, measured in semitones.

(2) *CVC:* The target and reference stimuli differed by the initial phoneme. The test contained 9 levels of perceptual distance between target and reference stimuli. Perceptual distance between phonemes was estimated based on phoneme confusability (Miller & Nicely, 1954) – the rates at which phonemes are misidentified. The first 5 test levels used between phonemic category changes, ranging from maximal perceptual distances (e.g.,/p/-/sh/ , level 9) to minimal differences (e.g.,/p/-/k/level 5). Control participants performed at ceiling when discriminating between all phoneme category contrasts. Therefore, the final four test levels used within-category contrasts. Stimuli for level 4 to 1 were created in Praat (www.praat.org). The PSOLA algorithm was used to make ten stage continua between/p-b/and/k-p/; stage 1 and 10 of the continuum being prototypical exemplars of the phoneme. The greatest within-category acoustic difference occurred between stage 1 and 5 or stage 10 and 6 of the continua, this difference was presented on Level 4 of the discrimination test. The smallest within-category acoustic difference occurred between stages 1 and 2 or 10 and 9 of the continua; this difference was presented on Level 1 of the discrimination test.

#### 2.3.2. MMN paradigm

Threshold results from behavioural testing were used to develop multiple deviant MMN paradigms containing standard, deviant-above and deviant-below stimuli; parameters are displayed in Table 2. Within each group all participants were exposed to the same stimuli. The PT MMN stimuli were the same for the WA and control group; a 5 semitones change from standard to deviant was consistently perceptible to all participants (deviant-above change) and a change of .1 semitones was consistently non-perceptible to all participants (deviant-below change). In the WA group, the consistently perceptible CVC changes (deviant-above) were at the lowest levels of confusability (level 9 of the discrimination test e.g.,/kɔ:b/-/sɔ:b/) and consistently non-perceptible changes (deviant-below) occurred with the most confusable between phonemic category changes (level 5 of the discrimination test e.g.,/kɔ:b/-/pɔ:b/). The same between category changes were consistently perceptible to all control participants and were selected as the deviant-above stimuli for the controls. Within-category changes, equivalent to level 2 of the phoneme discrimination tests, were consistently non-perceptible to the control group and these changes were assigned to the deviant-below changes. MMN stimuli were presented binaurally at an intensity of 78 dB SPL. In each condition (PT and CVC), standard stimuli were presented on 65% of occurrences and each deviant type was presented 17.5% of occurrences; standard, deviant-above and deviant-below stimuli were presented in the same run. A total of 260 deviant stimuli were presented in each condition; 130 deviant-above and 130 deviant-below. The order of occurrence was pseudo-randomised so that at least one standard stimulus occurred between each deviant. Inter-stimulus onset-interval was jittered between 550 msec and 750 msec in the PT condition and between 750 msec and 950 msec in the CVC condition; i.e., the minimum time between PT stimulus onset was 550 msec and maximum time was 750 msec. Within each condition, three different standard-deviants contrasts were used and presented in separate runs; this aimed to reduce habituation. Fifteen standard stimuli were presented before the start of each run to establish familiarity; these were discarded for analysis. In addition, the deviant stimuli were presented in a deviant-alone condition containing only repeated "deviant" stimuli. This design allowed comparison of the same stimuli when they were presented as deviants in the oddball condition and when they were presented as standards in the deviant alone condition. During data collection, participants were instructed to remain still and to watch a silent nature programme, data collection took no longer than 1 h including the breaks, the length of which were was dictated by the participant.

#### 2.3.3. EEG acquisition and pre-processing

EEG data were collected with a 64 electrode BioSemi ActiveTwo system and ActiView acquisition software (Biosemi, Netherlands). Four external electrodes monitored horizontal and vertical eye movements. Online referencing was undertaken with the biosemi feedback loop system (cf. http://www.biosemi.com/faq/cms&drl.htm). ERP pre-processing, averaging and analysis was undertaken in EEGlab version 12

**Table 2 – Multiple deviant paradigm stimuli parameters.**

| | Run no. | Standard | Control | | WA | | Length (msec) | ISI range (msec) | Intensity (dB SLP) |
|---|---|---|---|---|---|---|---|---|---|
| | | | Bel | Abv | Bel | Abv | | | |
| PT (Hz) | 1 | 500 | 502.9 | 667.4 | 502.9 | 667.4 | 150 | 550–750 | 78 |
| | 2 | 650 | 646.3 | 486.9 | 646.3 | 486.9 | | | |
| | 3 | 800 | 804.6 | 1067.9 | 804.6 | 1067.9 | | | |
| CVC | 1 | keb | keb* | peb | peb | beb | 350 | 750–950 | 78 |
| | 2 | prob | prob* | korb | korb | vorb | | | |
| | 3 | korb | korb* | porb | prob | sorb | | | |

* Indicates within-category change from standard stimulus.

(Delorme & Makeig, 2004). The continuous EEG data were bandpass filtered, 2–40 Hz, and epoched from −100 msec to the minimum ISI length in each condition. Independent components analysis was performed (using the runica algorithm from EEGLAB) and eye movement related components subtracted. Epochs containing artefacts of ±120 μV were rejected. The average number of accepted epochs did not drop below 78% (102 trials) at the group level for any stimulus type. In the WA group participant DMC had the most epochs rejected with 53 epochs surviving pre-processing in the CVC deviant-below condition. In the control group, participant RM had the most rejected epochs with 76 surviving in the CVC standard-above condition (deviant alone deviant-above). Two-tailed *t*-tests did not reveal any group differences for the number of epochs surviving pre-processing except for in the CVC standard-above condition where there were significantly more accepted epochs in the WA than control group ($t_{(12)} = 2.5$, $p = .03$).

### 2.4. *Statistical analysis*

MMN difference waves were produced for each standard-deviant pair by subtracting the deviant-alone epochs from the oddball deviant epochs, creating three above-deviant and three below-deviant difference waves in each condition. MMN peaks were visually identified in each difference wave as the first negative deflection with a fronto-central topology following the deviant alone P1–N1 complex. A MMN could be identified for the majority but not all runs. The PT deviant-below difference waves produced the fewest MMNs (MMNs identified in 76% control runs and 81% WA runs), followed by the deviant-above difference waves in the WA CVC condition (86% runs with identifiable MMNs) and the deviant-below difference waves in the CVC condition (MMNs identified in 90% runs in both groups). MMNs were identifiable in the PT deviant-above difference waves in all but one run in control participant RM where no MMN peak could be identified, the data values were set to zero for all subsequent ERP analysis. Difference waves were then re-centred so that MMN peak was at the same time point, t = 0 msec.

For each difference wave, mean MMN amplitude (20 msec surrounding the MMN peak) and peak amplitude values were extracted from six fronto-central electrodes (Fz, FCz, F1, FC1, F2, FC2), four left lateralised frontal electrodes (F3, FC3, F5, FC5) and four right lateralised frontal electrodes (F4, FC4, F6, FC6). Data from the electrode sets were averaged for each run and the above-deviant and below-deviant runs were averaged separately within each condition. A lateralisation index was calculated for the mean amplitude and "peak" amplitude values from the left and right sensors to indicate the relative strength of response in each hemisphere. Peak amplitude from these sensor sets was taken from the same time point as the fronto-central sensor set. The lateralisation index is calculated as *(left peak − right peak)/(left peak + right peak)*; an index value of −1 indicates entirely right hemisphere lateralised response and an index value of +1 indicates entirely left lateralised response (Seghier, 2008). In addition, peak latency values were extracted from the fronto-central sensors.

Statistical analysis of MMN morphology (amplitude and latency) used 2 × 2 × 2 ANCOVAs, Group (WA *vs* control) × Condition (PT *vs* CVC) × Perceptibility (above *vs* below), co-varied for mean peripheral hearing threshold. Mean hearing threshold was calculated as the average pure tone audiometry thresholds at 500 Hz, 1 kHz, 2 kHz and 4 kHz for the right and left ears. ANCOVAs were run on the mean and peak amplitude and peak latency values from the fronto-central electrodes. Partial correlations, controlling for hearing, were run between behavioural measures and corresponding MMN measures within each group. Analysis co-varied for hearing because hearing level has been observed to impact MMN amplitude (Oates, Kurtzberg, & Stapells, 2002) and the current study found a significant interaction between hearing and ERP morphology (see Results).

## 3. Results

### 3.1. *Behavioural results*

Auditory threshold results, group differences and single subject analysis are presented in Table 3. The WA and control group did not significantly differ on frequency discrimination thresholds; however two WA participants' thresholds (DR and LS) were outside normal limits. The WA group displayed significantly elevated CVC thresholds (CVC: $t_{(12)} = 4.4$, $p = .001$), all WA participants were outside normal limits based on Crawford and Garthwaite's (2007) Bayesian method.

### 3.2. *EEG results*

#### 3.2.1. *MMN waves and scalp distributions*

MMN difference waves and scalp amplitude distributions surrounding the MMN peak are displayed in Figs. 2 and 3. The scalp distributions showed consistently more widespread negative amplitudes to deviant-above than deviant-below

**Table 3 – Behavioural discrimination results.**

| | Participant | Threshold | |
|---|---|---|---|
| | | Frequency difference | CVC difference |
| WA | DR | *2.70* | *8.50* |
| | DL | .43 | *7.00* |
| | DMC | .30 | *5.00* |
| | MR | .80 | *5.75* |
| | EL | .75 | *5.50* |
| | CW | .60 | *6.00* |
| | LS | *1.80* | *6.75* |
| | Mean | 1.05 | 6.36 |
| | SD. | .87 | 1.17 |
| Control | DW | .63 | 3.50 |
| | DO | .40 | 4.00 |
| | RM | .27 | 4.70 |
| | CR | .43 | 4.00 |
| | BR | 0.2 | 4.75 |
| | PL | .97 | 2.75 |
| | PT | 1.50 | 4.75 |
| | Mean | .60 | 4.06 |
| | SD. | .49 | .75 |
| *t* test | *t* value | 1.19 | 4.4 |
| | *p* value | ns | .001 |

NB: *Italics* indicate outside normal limits based on control data.

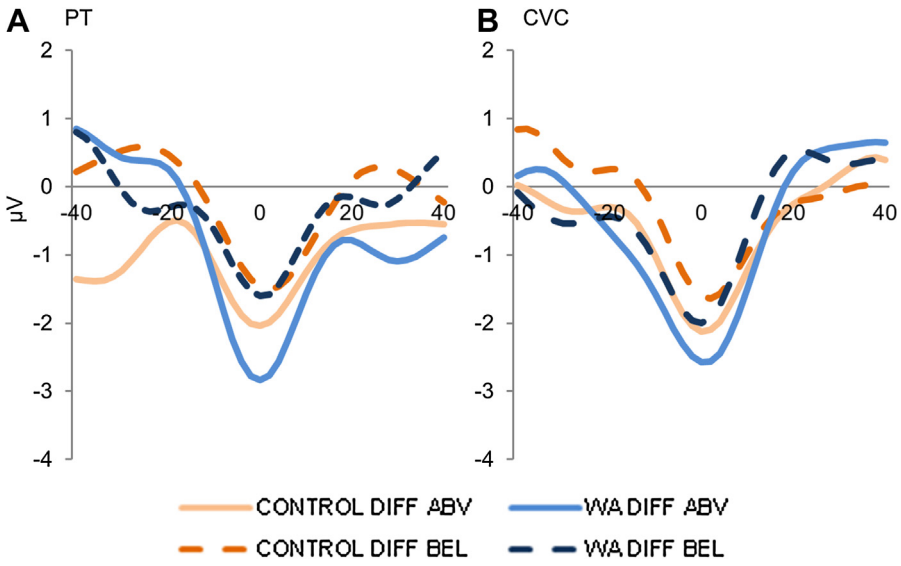


**Fig. 2 – Mismatch Negativity Difference Waves. Difference waves (oddball deviant minus deviant alone) displayed for the 80 msec window surrounding the MMN peak. Participants MMN peaks have been re-centred to time = 0 msec (*x* axis). A. Pure tone contrasts, B. CVC contrasts.**

stimuli. In the CVC condition, the WA group showed a slight rightward skew to deviant-above stimuli in comparison to the deviant-below stimuli. Deviant-below CVC stimuli produced a non-standard, weak MMN topology in the control group and a central negativity in the WA group.

### 3.2.2. *ERP analysis*

Fronto-central electrode set peak and mean amplitude and peak latency are provided in Table 4 alongside peak and mean lateralisation index values. Further peak and mean amplitude values for the left and right electrode sets are provided in

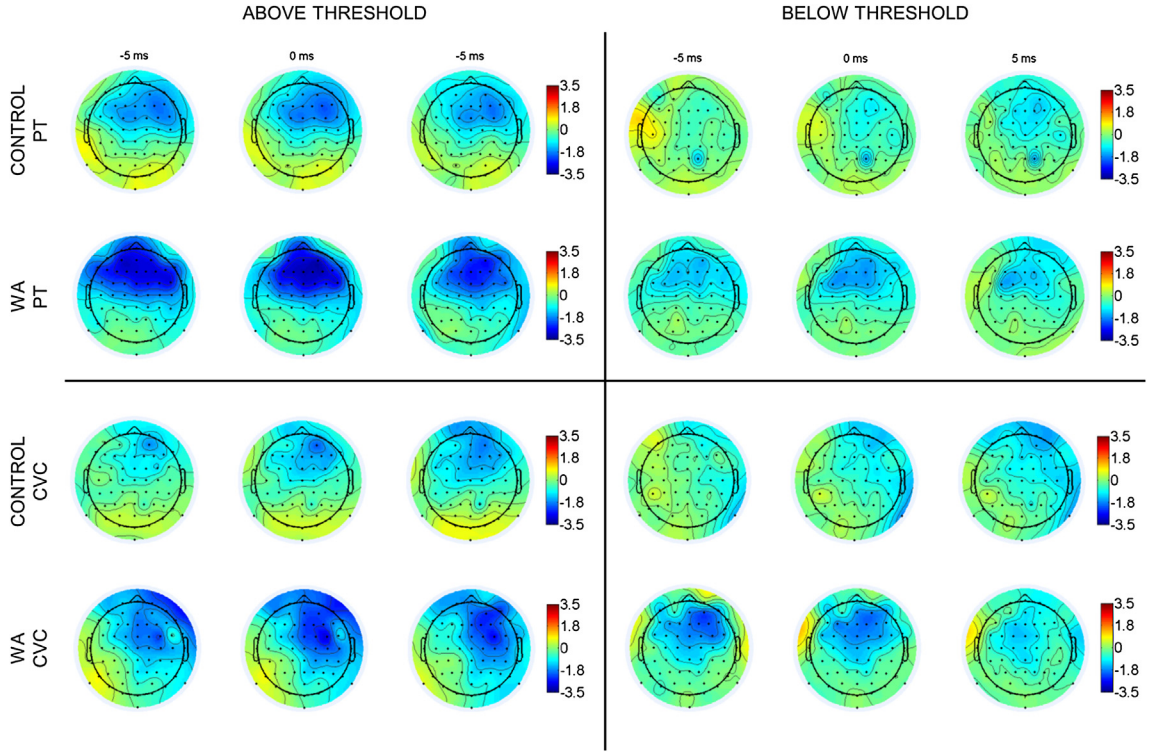


**Fig. 3 – Topography Distribution of MMN Difference Peaks. Topography plots displayed for the MMN difference wave peak (0 msec), 5 msec prior to the peak and 5 msec following the peak. Only runs with identifiable peaks are included in topography analysis. Left column displays above threshold contrasts and right column displays below threshold contrasts. Top panel displays pure tone condition and bottom panel displays CVC condition.**

**Table 4 – MMN morphology data.**

| | | PT | | CVC | |
|---|---|---|---|---|---|
| | | Abv | Bel | Abv | Bel |
| Control | Peak (μV) | −2.1 (.86) | −1.61 (.62) | −2.14 (1.05) | −1.47 (.69) |
| | Mean (μV) | −1.66 (.70) | −1.06 (.60) | −1.65 (1.04) | −.96 (.67) |
| | Latency (ms) | 160 (13.0) | 159 (13.9) | 160 (35) | 170 (26) |
| | LI peak | −.036 (.070) | −.009 (.010) | −.043 (.053) | −.009 (.048) |
| | LI mean | −.039 (.067) | −.003 (.017) | −.045 (.055) | −.01 (.043) |
| WA | Peak (μV) | −2.84 (.92) | −1.62 (.63) | −2.66 (.67) | −2.05 (1.18) |
| | Mean (μV) | −2.18 (.84) | −1.17 (.62) | −2.10 (.75) | −1.52 (1.12) |
| | Latency (ms) | 153 (22.5) | 151 (20.8) | 199 (42.0) | 183 (38.3) |
| | LI peak | −.037 (.037) | −.013 (.069) | −.055 (.057) | −.014 (.095) |
| | LI mean | −.030 (.026) | −.008 (.052) | −.043 (.041) | −.049 (.045) |

LI = laterality index: +1 corresponds to purely left lateralised response, −1 corresponds to purely right lateralised response.

supplementary materials Tables S1 and S2. ANCOVA analyses (see Methods, Statistical Analysis) revealed a main effect of condition for peak amplitude ($F_{(1,11)} = 6.16$, $p = .030$) caused by small but significantly greater peak amplitude overall in the CVC condition than the PT condition.

Perceptibility differences were observed in the amplitude data in the PT condition. Significant interactions between condition and perceptibility were found in the amplitude ANCOVAs (peak: $F_{(1,11)} = 4.88$, $p = .049$; mean: $F_{(1,11)} = 5.14$, $p = .044$) caused by significantly greater amplitude in the deviant-above than deviant-below PT condition (peak: $t_{(26)} = -2.87$, $p = .008$; mean: $t_{(26)} = -3.02$, $p = .006$) but not the CVC condition.

The WA and control group were only distinguished by response latency. A significant group-x-condition interaction was found for peak latency ($F_{(1,11)} = 7.1$, $p = .022$), caused by longer peak latency for the CVC condition in the WA group (Fig. 4). The CVC stimuli differed between the WA and control group, reflecting significant differences in behavioural discrimination capacity. In order to ensure a perceptible acoustic change in the WA deviant-above condition, a salient plosive-fricative contrast was used (e.g., prob-sorb). This was in comparison to the plosive–plosive contrasts used in the control group (e.g., porb-korb). Although the stimuli were matched for length overall, the plosive-fricative contrasts have a longer point of difference between the standard and deviant than the plosive–plosive contrasts. Therefore, in order to ensure the group-x-condition latency interaction was not a stimulus effect, a 2 × 2 Group-×-Condition ANCOVA was performed on the latency values from standard-deviant contrasts that were the same in each group, i.e., the deviant-above PT stimuli for both groups and the deviant-below CVC stimuli in the WA group and deviant-above CVC stimuli in the control group. This analysis also found a significant group-×-condition interaction ($F_{(1,11)} = 5.63$, $p = .037$) and an additional main effect of condition ($F_{(1,11)} = 6.35$, $p = .028$), confirming that MMN latency was significantly longer in the WA than control group for the CVC stimuli only (PT: $t_{(26)} = 1.1$, $p = .29$; CVC $t_{(26)} = -2.03$, $p = .052$).

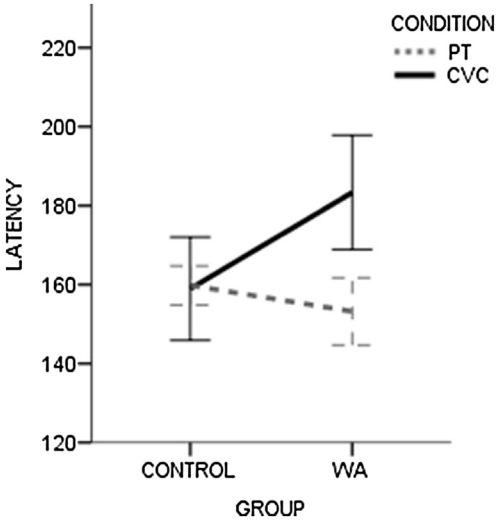


**Fig. 4 – Group × Condition Interaction for MMN Peak Latency. Mean MMN peak latency for the control and WA groups in the CVC condition (collapsed over deviant-above and deviant-below stimuli).**

The peak amplitude ANCOVA analysis displayed a significant two-way interaction between condition and the mean hearing covariate (peak: $F_{(1,11)} = 6.35$, $p = .028$) and a significant three-way interaction between condition, perceptibility and mean hearing were observed for peak and mean amplitude (peak: $F_{(1,11)} = 6.13$, $p = .031$; mean $F_{(1,11)} = 6.29$, $p = .029$). These interactions were caused by a significant association between hearing and amplitude in the PT deviant-above condition (peak: $r = -.657$, $p = .011$; mean: $r = -.597$, $p = .024$). No other main effects or interactions were found for the mean amplitude results.

Partial correlations, co-varied for mean hearing, showed a relationship between PT MMN deviant-above latency and PT discrimination thresholds in the control group ($r = .97$, $p = .002$[1]) but not in the WA group. There were no associations between PT MMN amplitude and behavioural assessments in either group.

Behavioural CVC discrimination thresholds correlated significantly with the mean amplitude of *deviant-below* CVC stimuli in both groups (control mean: $r = .88$, $p = .019$; WA mean: $r = -.89$, $p = .017$). However, the direction of effect was different between the groups. The control group showed a

[1] Correlations surviving Bonferroni correction based on the number of correlations performed within condition and within group.

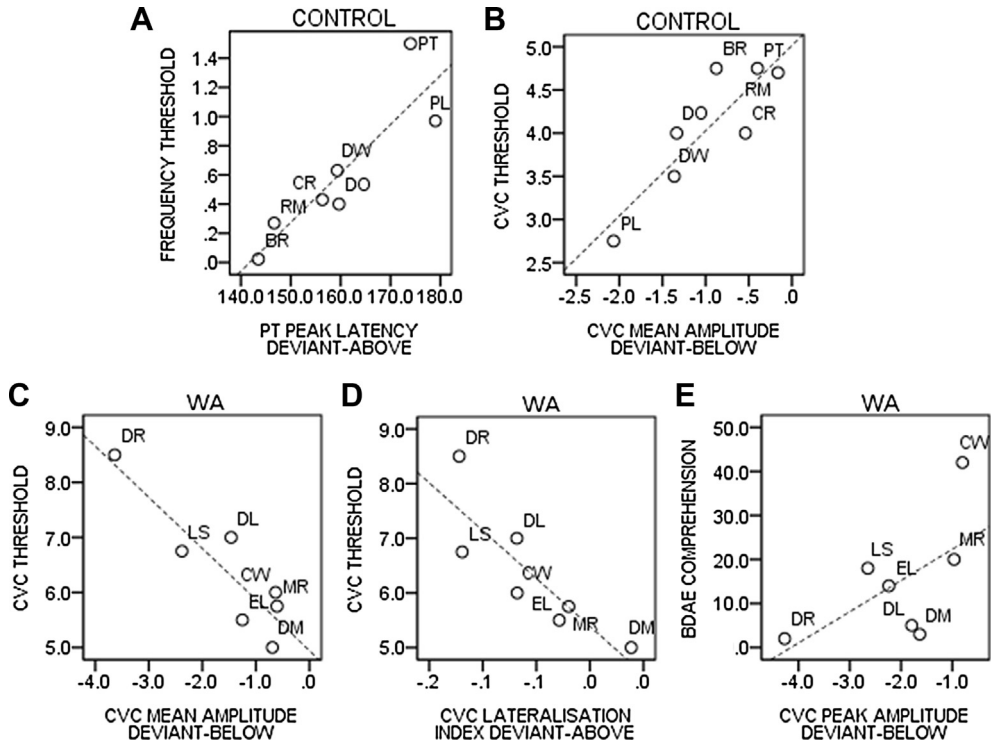


**Fig. 5 – Correlations between CVC Discrimination Threshold and CVC MMN Responses. Scatter plots displaying correlations between behavioural measures and MMN features. For frequency and CVC thresholds smaller values indicate better discrimination. A. Significant correlation between MMN PT latency to deviant-above stimuli and frequency discrimination in control participants – shorter response latency corresponding to better discrimination. B. Significant correlation between CVC MMN amplitude to deviant-below stimuli and CVC discrimination in control participants – greater amplitude corresponding to better discrimination. C. Significant correlation between CVC MMN amplitude to deviant-below stimuli and CVC discrimination in WA participants – greater amplitude corresponding to worse discrimination D. Significant correlation between lateralisation index (LI) of CVC MMN response to deviant-above stimuli and CVC discrimination thresholds in WA participants. E. Significant correlation between BDAE auditory comprehension scores and CVC MMN amplitude to deviant-below stimuli.**

direct correlation where the greater the MMN amplitude, the better the behavioural discrimination. The WA showed an inverse correlation where the greater the MMN amplitude, the poorer the behavioural discrimination. The WA group but not the control group also showed a significant correlation between behavioural CVC discrimination thresholds and the laterality index of deviant-above CVC peak amplitude ($r = -.941$, $p = .005$[1]); the less right hemisphere dominance, the better the discrimination (see Fig. 5 for correlations with CVC behavioural thresholds). Finally, the WA group showed a significant relationship between language comprehension scores (as measured on the BDAE; Goodglass et al., 2001) and MMN amplitude to CVC deviant-below stimuli (peak: $r = .95$, $p = .003$[1]; mean: $r = .89$, $p = .018$) the *greater* the MMN peak, the *lower* the comprehension score. Correlation results for all permutations are presented in supplementary materials Tables S3 and S4.

## 4. Discussion

This study explored neural responses corresponding to different degrees of behavioural auditory discrimination accuracy in WA and how these responses reflect the neuropsychological profile. The results revealed significantly increased MMN response latencies to CVC changes in the WA group compared to the control group and a number of significant correlations between CVC MMN morphology and behavioural profiles in both groups. However, no significant MMN morphological differences were found between auditory changes of different perceptibility.

### 4.1. *Differentiating behavioural discrimination accuracy*

The primary aim of this study was to investigate neural responses corresponding to impaired and intact phonological discrimination in WA. This was compared to an analogous condition in a control group, investigating responses to within – and between – phonological category changes. It was hypothesised that, if impairments in phonological discrimination in WA arose because of an inability to detect subtle acoustic differences, then no MMN would be detected to CVC changes below the perceptual threshold. On the other hand, if impairments arose because of inefficiencies in hierarchical auditory processing, then MMN components should be

present to non-perceptible CVC changes, but with altered morphology. Neither of these predictions were completely realised in the study; however, taken in the context of current auditory processing models, the lesion, behavioural and MMN evidence together indicate inefficiencies in hierarchical processing as a likely cause of behavioural auditory processing impairments in WA.

That a MMN was detected in the deviant-below/below perceptual threshold condition indicates that early stages in the auditory network had analysed these stimuli to a sufficient resolution for acoustic change to be detected. The human auditory network is able to discriminate tone/chord changes which are considerably smaller than the estimated bandwidth of peripheral sensors. Neurons in the auditory cortex have shown frequency tuning at narrow bandwidths and the integration of populations of these neurons is estimated to allow for discrimination of frequency changes smaller than those detected behaviourally by naïve listeners (Bitterman et al., 2008); this is likely to be the source of the MMNs in the PT deviant-below condition in both groups. CVCs are more complex acoustic stimuli containing multiple auditory cues. As such, auditory responses are produced by wider regions in the auditory network, by multiple spectro-temporal response fields, sensitive to different acoustic elements (Chevillet, Riesenhuber, & Rauschecker, 2011). Indeed, overall, the MMNs in the CVC condition were of greater magnitude than in the PT condition. This finding parallels previous literature which has found wider neural response networks to phonetic than chord changes (Tervaniemi et al., 2000). It is worth noting that, because CVC stimuli contain acoustic components both relevant and non-relevant to phonological discrimination, the generation of a MMN in the deviant-below condition does not necessarily mean that acoustic changes required for phonetic identification have been analysed.

Despite MMN generation, behavioural discrimination is impaired or absent for the deviant-below changes in both groups. In the PT condition this was reflected by reduced amplitude to deviant-below stimuli compared to deviant-above over all participants and visual inspection of the scalp distributions indicated a reduced spread of negativity for the deviant-below stimuli for both groups. In the CVC condition no morphological feature statistically distinguished the deviant-above changes from the deviant-below changes, although, on average, for both groups and both stimuli types, the deviant-below produced MMNs of smaller amplitude (Table 4). The control group displayed a disorderly scalp distribution to the deviant-below CVC stimuli whereas the WA group displayed a more standard distribution to deviant-below stimuli but with reduced frontal and right hemisphere negativity in comparison to the deviant-above stimuli. It may be interesting to further explore these scalp distribution changes to investigate whether the inability to behaviourally perceive change is reflected by changes in network coherence; for example reduced coherence between temporal (auditory) and frontal (attentional) components. Previous MMN work in the neurologically normal population has also identified MMNs to within-category phonological changes (Dehaene-Lambertz, 1997; Sams, Aulanko, Aaltonen, & Näätänen, 1990); in some cases with reduced amplitudes, although the same MMN morphology as between category changes have been found when strict acoustic controls have been used (Sharma, Kraus, McGee, Carrell, & Nicol, 1993). It is proposed that, because within-category changes are not behaviourally relevant, top-down information can shape hierarchical processing and prevent their being identified as different stimuli (Davis & Johnsrude, 2007). In contrast, the CVC deviant-below changes in the WA group are behaviourally relevant and discriminable by the control group. We hypothesise that weakness in hierarchical processing and binding of decomposed acoustic features into invariant auditory objects abates the early auditory responses and prevents these phonological changes being detected. Given that lesions in WA partially disrupt left hemisphere auditory regions, it is logical to assume relatively greater reliance or input into the right hemisphere network. Although the right hemisphere responds to phonetic information, it has less sensitivity to this type of stimulus than the left hemisphere (DeWitt & Rauschecker, 2012). The right hemisphere has been proposed to preferentially respond to spectral information and temporal changes over longer time windows (Boemio, Fromm, Braun, & Poeppel, 2005; Poeppel, 2003; Zatorre & Belin, 2001). Small phonological changes encoded over short time scales, such as/p/-/k/, may be outside the resolution of this system and therefore differences are not maintained at later stages in the processing stream. Larger acoustic changes (such as in the WA CVC deviant-above condition) may be within the resolution of the system and, therefore, differences are maintained at later processing stages to a sufficient extent for behavioural discrimination to take place. This interpretation suggests that accurate phonological discrimination does not automatically correspond to accurate, fully specified, acoustic-phonological processing; but rather a sufficient maintenance of difference up to the point of interaction with executive and attention networks.

This hypothesis, of inefficiencies in hierarchical processing for phonetic stimuli, corresponds with the similarities and differences found between the groups. There were no MMN morphological feature differences between the WA and control groups for PT changes. This is consistent with behavioural evidence which has not found impairments in frequency discrimination in aphasia (Robin et al., 1990) and additional MMN evidence which has not found significant morphology alterations to frequency changes (Ilvonen et al., 2004; Pettigrew et al., 2005; Wertz et al., 1998). This indicates that both the control and aphasia groups are primarily relying on the same neural substrates for frequency discrimination, presumably (residual) right hemisphere regions. In the CVC condition, however, the WA group displayed significantly increased MMN latencies which remained when stimulus changes were matched in duration. This finding also replicates previous MMN studies in aphasia (Pettigrew et al., 2005) and has been interpreted as slowed auditory processing of speech stimuli. This finding may indicate that the WA and control groups have a primary reliance on different neural substrates for processing phonological information; the control group taking advantage of intact, efficient, left hemisphere regions and the WA group relying on support from less efficient right hemisphere regions to supplement the damaged left hemisphere. Of interest, the WA group showed a clearer fronto-central negative scalp distribution to the

deviant-below changes in both the PT and CVC than the control group. This may be expected in the CVC condition, where there is a greater acoustic difference in the deviant-below change in the WA than in the control group. However, this result is less interpretable for the PT condition as the stimuli changes were the same between the groups and if found to be consistent may warrant further investigation.

### 4.2. *ERP and behavioural correlations*

The second aim of this study was to investigate the relationship between MMN responses and behavioural profile. Previous studies involving aphasia participants with mixed subtypes have found some links between behavioural language profile and auditory ERPs, although the direction of correlation has been inconsistent. Aphasia severity has been found to correlate with amplitude (Pettigrew et al., 2005) and duration (Wertz et al., 1998) of MMNs induced by syllable changes; where increased amplitude and duration corresponded to better language processing. Conversely, Becker and Reinvang (2007) found that greater N1 amplitude to harmonically rich tones was related to poorer auditory comprehension outcomes following therapy. The current study found a number of similar, seemingly paradoxical, correlations in the WA group. These correlations, however, are interpretable in the light of the inefficient hierarchical processing hypothesis.

Both the control and WA group displayed significant correlations between CVC MMNs and behavioural scores. Behavioural CVC discrimination thresholds were significantly related to MMN amplitude in both groups, however, the effect direction was different. The effect in the control group was in the expected direction, that is, greater MMN amplitude correlated with lower (i.e., better) discrimination thresholds. The direction of the WA group was in the opposite direction; that is, the greater the MMN amplitude, the worse auditory discrimination. We interpret this as a reflection of the control group relying on an efficient processing pathway and the WA having to rely, to a greater extent, on a non-efficient system. In this case, increased response magnitude is beneficial for the control group because it is stems from well organised processing; whereas increased response magnitude is maladaptive in the WA group because it stems from inefficient processing. This interpretation corresponds well to the results of an elegant aphasia MMN study which employed magnetoencephalography and dynamic causal modelling with individuals with deficits in auditory comprehension and auditory processing (Teki et al., 2013). In their study, speech sound changes induced a bilateral up-regulation of feedforward connections from primary auditory regions to higher-order regions of the auditory ventral stream. This increased connectivity was not paralleled by an increase in within-region connectivity, an effect that was observed in control participants. Teki et al. (2013) interpreted these findings as a reflection of inefficient processing in aphasia, whereby noisy inputs are passed to higher-order ventral stream regions. The results from the current study fit with this interpretation, in that greater MMN amplitude corresponded to greater deficits, possibly indicating greater noise in the auditory network.

The current study additionally found a negative correlation between WA auditory comprehension scores and CVC MMN amplitude. This adds to behavioural evidence linking processing of speech and non-speech sounds to auditory comprehension skills in WA (Robson et al., 2013; Robson, Keidel, et al., 2012). This correlation also indicated that greater responses in an inefficient pathway correspond to greater auditory comprehension impairment. Interestingly, the above correlations were found with the MMN responses elicited by deviants below the perceptual discrimination threshold. We hypothesise that this is because the deviant-above changes are perceptually salient and processing of such changes does not place great strain on the auditory system. Deviant-below changes, however, are acoustically more similar and pose a greater challenge to the auditory processing system. The degree of early auditory response to these stimuli may be ultimately more reflective of the auditory discrimination thresholds, as the threshold reflects the level at which auditory processing is challenging, where differences are only just perceptible.

One exception was the correlation found between response latency to PT deviant-above changes and frequency discrimination thresholds in the control group, where earlier responses were detected in individuals with better auditory discrimination. A second exception was observed for the correlation between lateralisation of response to CVC *deviant-above* stimuli and CVC discrimination thresholds in the WA group; here better CVC discrimination was associated with more symmetrical or leftward responses. Overall, however, there was a strong contribution from right hemisphere sensors confirmed by visual inspection of topographic scalp distribution, which showed greater negativity over right than left parietal and temporal sensors (Fig. 3). Again, this result is in accordance with the results from Teki et al. (2013), who found a negative correlation between interhemispheric primary auditory cortex connectivity and CVC phonological discrimination scores; the greater the connectivity, the more impaired discrimination. Teki et al. (2013) interpreted their finding as an indication that greater functional segregation between hemispheres allowed each hemisphere to engage in specialised processing. Similarly, under the current hypothesis, the greater involvement of the left hemisphere substrates (more specialised for phonemic processing), the better the behavioural auditory discrimination.

### 4.3. *Conclusions*

This study used electrophysiology to investigate neural responses corresponding to behavioural auditory discrimination accuracy and inaccuracy in WA. The study found that MMNs were generated by stimuli that could not be behaviourally perceived, indicating weaknesses in hierarchical processing and poor processing and maintenance of early auditory responses. Further evidence indicated that greater response magnitude in an inefficient processing stream may have a maladaptive effect. The results from the current study could be used to evaluate therapy-induced changes in auditory discrimination accuracy.

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## Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.cortex.2014.07.009.

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