

Research Article

Rapid Increase in Neural Conduction Time in the Adult Human Auditory Brainstem Following Sudden Unilateral Deafness

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Received: 27 October 2014; Accepted: 20 May 2015; Online publication: 9 June 2015

ABSTRACT

Individuals with sudden unilateral deafness offer a unique opportunity to study plasticity of the binaural auditory system in adult humans. Stimulation of the intact ear results in increased activity in the auditory cortex. However, there are no reports of changes at sub-cortical levels in humans. Therefore, the aim of the present study was to investigate changes in sub-cortical activity immediately before and after the onset of surgically induced unilateral deafness in adult humans. Click-evoked auditory brainstem responses (ABRs) to stimulation of the healthy ear were recorded from ten adults during the course of translabyrinthine surgery for the removal of a unilateral acoustic neuroma. This surgical technique always results in abrupt deafferentation of the affected ear. The results revealed a rapid (within minutes) reduction in latency of wave V (mean pre=6.55 ms; mean post=6.15 ms; $p<0.001$). A latency reduction was also observed for wave III (mean pre=4.40 ms; mean post=4.13 ms; $p<0.001$). These reductions in response latency are consistent with functional changes including disinhibition or/and more rapid intra-cellular signalling affecting binaurally sensitive neurons in the central auditory system. The results are highly relevant for improved understanding of putative

physiological mechanisms underlying perceptual disorders such as tinnitus and hyperacusis.

Keywords: disinhibition, deafferentation, auditory brainstem response, unilateral deafness, acoustic neuroma, neural plasticity

INTRODUCTION

Damage to a sensory system triggers a change in neural representation of the sense via injury-induced plasticity (for a review, see Buonomano and Merzenich 1998). These neural changes are thought to underlie sensory disorders such as neurogenic pain, phantom limbs and analogous hearing disorders such as tinnitus and hyperacusis (e.g. Rauschecker 1999; Salvi et al. 2000; Woolf and Salter 2000; Adjajian et al. 2009; Gu et al. 2010; Irvine 2010; Zeng 2013). An improved understanding of injury-induced plasticity might therefore lead to the development of interventions for the resulting perceptual disorders. In the auditory modality, numerous animal studies have described the pattern and time course of plasticity in various cortical and brainstem regions by inducing unilateral deafness (UD; for a review, see Moore and King 2004). However, analogous data on humans with UD is sparse and evidence for any changes is limited to

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observation of activity in the auditory cortex (for a review of cortical findings, see Thai-Van 2013). To date, there is no evidence for any changes in the auditory brainstem. Therefore, the primary aim of the present study was to investigate injury-induced plasticity in the brainstem of adult humans with UD.

Experimentally induced UD in adult animals leads to increased neural responsiveness to stimulation of the intact ear (Popelar et al. 1994; McAlpine et al. 1997; Mossop et al. 2000). The changes are greatest in the pathway ipsilateral to the intact ear, probably because this pathway normally receives the strongest input from the deafferented ear (Adams 1979; Coleman and Clerici 1987). Similar findings have also been shown to occur at the level of the auditory cortex in adult humans with injury-induced UD (Scheffler et al. 1998; Bilecen et al. 2000; Ponton et al. 2001; Langers et al. 2005; Firszt et al. 2006; Maslin et al. 2013a, b).

Two studies have investigated sub-cortical plasticity in humans with UD, and neither has successfully replicated the findings of the animal studies. Vasama et al. (2001) measured sub-cortical activity using the auditory brainstem response (ABR). The ABR is a series of sound-evoked potentials or 'waves', arising from the auditory nerve, brainstem and midbrain, which can be detected via surface electrodes. The latencies of the ABR waves, reflecting neural conduction velocity and synaptic efficiency, were recorded in seven individuals before and after surgical removal of a unilateral acoustic neuroma. An acoustic neuroma is a benign space-occupying tumour of the eighth cranial nerve. Surgical removal, using the translabyrinthine approach, involves deafferentation of the operated ear and therefore results in an abrupt and total loss of hearing in that ear (Ramsden 1995; Leonetti and Marzo 1999). Furthermore, this deafferentation is similar to experimentally induced deafness in animals (although the presence of the acoustic neuroma itself often leads to partial hearing loss in the affected ear prior to surgery). Based on the findings from animal studies, a predicted increase in responsiveness to stimulation of the intact ear should be reflected by a decrease in the ABR latency and an increase in ABR amplitude (Popelar et al. 1994). However, the post-surgery ABR latencies reported by Vasama et al. (2001) were not statistically different from the pre-surgery baseline measures or those of a binaurally hearing control group, while amplitudes were not reported. Langers et al. (2005) used functional magnetic resonance imaging (fMRI) to investigate cortical and sub-cortical auditory-evoked activity in five individuals with UD and eight binaurally hearing controls (Langers et al. 2005). An increase in cortical activity was observed in the UD participants (primarily on the hemisphere ipsilateral

to the intact ear), but there was no difference in sub-cortical activity between the groups.

The reason for the null findings reported in these two studies is unclear, although the most parsimonious explanation relates to methodological factors. In terms of the extent of deafness, Vasama et al. (2001) used a heterogeneous group of participants; of the seven individuals who underwent surgery, three benefitted from surgical techniques which allowed preservation of hearing on the affected ear and one participant already had a longstanding complete UD prior to the surgery. Therefore, the impact of the surgery might have been reduced in these four participants. The lack of changes reported by Langers et al. (2005) may have been due to the comparatively lower fMRI signal to noise ratio (due to close proximity of bone and air-filled cavities and sources of vascular noise) that could be obtained from sub-cortical regions of the auditory system. In addition, the fMRI data were not corrected for cardiac-related pulsatile brainstem motion, reducing experimental sensitivity (Guimaraes et al. 1998).

Another area for further investigation in adult humans is the time course of events at both cortical and sub-cortical levels. Different physiological mechanisms, or combinations of mechanisms, are likely to follow different time courses (Irvine 2010). There are two general mechanisms by which the efficacy of input from the intact ear could change. The first is rapid functional changes to the existing neural architecture. Functional increases in responsiveness to the intact ear may derive from inactivation of inhibitory pathways that are normally driven by the deafened ear, resulting in 'unmasking' of pre-existing excitatory connections. These changes may involve intracellular signalling pathways that increase or decrease the gain of existing excitatory neurons and synapses (McAlpine et al. 1997; Mossop et al. 2000; Moore and King 2004). The second mechanism is relatively slow structural changes involving elimination of synapses and expression of new synapses and/or axons (Moore 1994; McAlpine et al. 1997). Evidence from animals with experimentally induced UD indicates that increased neural responsiveness to stimulation of the intact ear occurs over a wide time frame. Initial increases in excitatory responses of cortical and sub-cortical neurons have been demonstrated within minutes to hours post-UD (Popelar et al. 1994; Mossop et al. 2000), while further changes have been observed a number of months post-UD (McAlpine et al. 1997). Therefore, the data from animal studies are consistent with a cascade of multiple processes driving plasticity.

In contrast to animal studies, evidence showing the time course of injury-induced plasticity in humans is sparse. A few studies have measured cortical activity

longitudinally after surgically induced UD. The results from these studies indicate that increased cortical responsiveness occurs within 1 week and continues for at least 6 months post-surgery (Bilecen et al. 2000; Maslin et al. 2013b). However, these data focus exclusively on the time course of changes in cortical activity and provide no information about changes in sub-cortical activity. Moreover, the precise point in time when injury-induced CAS plasticity commences could not be determined from these studies due to the need for a recovery period from general anaesthesia before cortical recordings could be obtained.

The practical limitations governing the timing of initial investigations into plasticity in humans after surgically induced UD can be overcome by conducting investigations of the brainstem intra-operatively. Although cortical evoked responses are abolished by anaesthesia, ABRs are generally unaffected (Moller 2010). Therefore, patients undergoing translabyrinthine surgery for acoustic neuroma removal present a unique opportunity to study the immediate response of the human brainstem to UD, in a manner analogous to studies on animals (Popelar et al. 1994; Mossop et al. 2000).

The primary aim of the present study was to investigate the effect of UD on the human auditory brainstem. Since the prolonged imbalance of sensory input to neurons sensitive to input from either ear is thought to trigger plasticity of binaural systems (Moore and King 2004), it was hypothesised that the ABR latencies would decrease, and amplitude would increase, for latencies beyond wave III because this is thought to be the earliest point where binaurally sensitive neural generators contribute to the overall response (Levine 1981). Responses at earlier latencies (such as waves I and II) are thought to be generated by the auditory nerve (Moller and Jannetta 1981) and should not be directly affected by deafening of the opposite ear. However, it could be that efferent system involvement causes changes at wave III and earlier. Therefore, no specific predictions were made with regard to changes in latency of these earlier waves. A second aim was to investigate the speed of any neural changes. It was hypothesised that any changes would commence rapidly after the deafferentation and therefore be apparent as soon as the experimental conditions allowed.

METHODS

Participants

Participants were ten adults undergoing translabyrinthine surgery (resulting in complete sectioning of the auditory nerve) for unilateral acoustic neuroma removal (five male, five female, 30–77 years,

mean=53 years). Table 1 shows the individual characteristics of each participant prior to surgery. The mean inter-aural threshold asymmetry (based on each participant's mean threshold between 500 and 4000 Hz) was 28 dB (range=2–59 dB). Tumours were either located entirely within the internal auditory canal ($n=4$) and causing no brainstem compression (intra-canalicular (IC)) or were occupying space in the cerebellopontine angle ($n=6$), potentially causing a degree of brainstem compression (extra-canalicular (EC)). Acoustic neuromas are, by convention, classified according to their size, with <1.0-cm diameter over its longest dimension as 'small', 1.0- to 2.5-cm diameter as 'medium' and >2.5-cm diameter as 'large' (Moffat et al. 1989). Mean tumour size was 1.3-cm diameter over its longest dimension (range=0.5 to 1.8 cm). There were six left-sided tumours and four right-sided tumours. The mean duration of surgery was 8.5 h (range=6 to 11 h), comprising approximately 2.5 h pre-labyrinthectomy before abrupt hearing loss and approximately 6 h post-labyrinthectomy. The study was conducted in accordance with the declaration of Helsinki, and all participants gave written informed consent. The study was approved by the Greater Manchester East NHS Research Ethics Committee (12/NW/0695).

Recording Procedures

Participants were prepared for surgery by being placed in a supine position with the head turned approximately 45° so that the operated ear was tilted upwards. Data collection commenced when the participant was under anaesthesia. The sequential steps of the surgical procedure include initial incisions, cortical mastoidectomy, labyrinthectomy (the point at which complete deafness occurs), dura incision, tumour removal, harvesting of abdominal fat used to obliterate the defect and soft tissue closure (Leonetti and Marzo 1999). Care was taken to record data only during periods where cutting burrs and electrosurgical equipment were not in use (e.g. during saline irrigation) in order to minimise acoustical and electrical interference. Core body temperature was recorded at intervals across the 8–9 h of surgery using a temperature probe positioned in the distal oesophagus. Recordings were used to assess any potential effect of fluctuations in intra-operative core body temperature on ABR latencies (via neural conduction velocities). Core body temperature often drops at the beginning of surgery (due to the reduced ability of the body to homeostatically regulate temperature following anaesthesia, as a result of vasodilation) and is then brought back to normal with a heat blanket. Table 2 shows that the mean temperature at the start of surgery was 36.0 °C (range 35.4 to 36.7).

TABLE 1

Demographic characteristics of unilaterally deaf listeners

Age (years)	Sex	Size (cm)	Location	Ear	250	500	1000	2000	3000	4000	6000	8000
40	M	1.8	IC/CPA	L (tumour)	20	15	20	25	25	30	40	50
				R (test)	15	10	10	10	15	15	20	20
50	F	1	IC	L (tumour)	55	45	50	55	75	75	80	65
				R (test)	25	25	20	30	30	25	30	30
77	M	1.5	IC/CPA	L (tumour)	80	75	70	60	65	80	85	70
				R (test)	15	10	5	5	25	60	65	60
30	F	1	IV	L (test)	5	0	0	5	10	5	0	5
				R (tumour)	0	5	5	0	0	0	5	5
55	F	0.8	IC	L (test)	30	25	25	45	55	65	55	55
				R (tumour)	25	15	15	25	45	55	55	65
50	M	2	IC/CPA	L (tumour)	35	40	55	60	65	65	80	95
				R (test)	15	20	25	20	25	40	60	50
64	M	0.7	IC/CPA	L (tumour)	95	75	70	75	100	100	100	100
				R (test)	20	15	10	20	35	45	40	35
50	F	2	IC/CPA	L (test)	5	10	5	0	0	5	10	10
				R (tumour)	20	30	40	40	55	45	50	60
50	M	0.5	IC	L (tumour)	15	15	5	10	15	20	20	25
				R (test)	0	0	0	5	0	10	15	20
60	F	2	IC/CPA	L (test)	20	25	20	20	30	35	40	40
				R (tumour)	50	50	60	70	65	45	50	50

Age (years); sex (M/F); tumour size (cm); tumour location (IC internal canal, CPA cerebellopontine angle); tumour ear (R/L); audiometric thresholds from 250 to 8000 Hz

The mean temperature measured closest to the time of the labyrinthectomy (usually within 30 min) was 36.2 °C (range 35.7 to 36.8).

Stimuli, Recording Parameters and Analyses

The ABR was measured using an Interacoustics EP-25 clinical evoked potential system. Disposable silver/silver-chloride electrodes were placed on the high forehead (Fpz; positive) and the mastoid (negative) of the test ear. A ground electrode was placed above the right eye. Electrode impedances were maintained at ≤ 3 k Ω . Stimuli consisted of 0.1-ms alternating rectan-

gular clicks, presented to the test ear at a rate of 11.1 Hz, via an EarTone 3A insert transducer. The stimulus level was 60 dB nHL (equivalent to 95.5 dB peSPL in the occluded ear simulator). Responses were recorded with a sampling rate of 30 kHz. The recording window was 0 to 15 ms relative to stimulus onset, the amplifier gain was 86 dB, band-pass filtering was 100–3000 Hz, and artifact rejection levels were ± 40 μ V. Investigation of the time course was carried out by dividing data into six 1-h time bins, three of which were pre- and three post-deafferentation. The time bins corresponded to data collection commencing at -3, -2, -1, 0, +1 and +2 h relative to the labyrinthectomy [i.e. from the point at which the inner ear is completely destroyed and the individual will lose all hearing and vestibular function in the operated ear]. The approach taken was to compile the maximum number of epochs possible within each time bin in order to achieve the best possible signal to noise ratio. The total compiled in each time bin was variable, as it depended upon how often the electro-surgical equipment was in use. The mean number of accepted epochs measured in each time bin was 10,400 [1 s.d.=7600].

The accepted epochs were exported for offline analysis in Scan v4.3 (Neuroscan™). Offline analysis consisted of digitally filtering the data from 1 to 3000 Hz, using a slope of 24 dB/Oct, and applying an automated peak detection algorithm. The peaks were also checked visually. The amplitude of the dominant waves (I, III and V) was measured with reference to the trough that followed them, while the latency of

TABLE 2

Body temperature (°C) for each participant at baseline, around the time of the labyrinthectomy and at the end of surgery

Participant	Baseline	Labyrinthectomy	End of surgery
1	35.8	35.8	37.0
2	36.1	36.1	36.8
3	36.0	36.6	37.5
4	36.0	36.3	37.6
5	36.7	36.8	37.2
6	36.2	36.4	37.6
7	35.7	35.8	36.8
8	36.2	36.2	36.2
9	35.4	35.7	37.4
10	36.2	36.1	38.3
Mean (± 1 s.d.)	36.0 (0.35)	36.2 (0.36)	37.2 (0.58)
Range	35.4–36.7	35.7–36.8	36.2–38.3

each of the waves was measured with reference to the stimulus onset. Although waves III and V were reliably measured in all participants, wave I was not always present. Where assumptions of parametric tests held true, mean differences in latency and amplitude values between pre- and post-labyrinthectomy conditions (± 1 s.d.) were assessed using repeated-measures ANOVA.

RESULTS

Figure 1 shows grand mean ABR waveforms for pre- and post-deafferentation. The morphology is typical for a click stimulus presented well above the hearing threshold. The waveform is dominated by wave V and a smaller amplitude wave III (around 6 and 4 ms, respectively, uncorrected for the 0.81-ms delay due to transmission of the stimulus along the 278 mm of the ER3A transducer tubing). A clear wave I was present in the ABR pre-deafferentation (around 2 ms), but this was less clear in the post-deafferentation ABR. The mean interpeak intervals at the start of surgery were 2.1, 1.9 and 4.0 ms for I-III, III-V and I-V, respectively. The mean latencies of waves I, III and V are shorter post-deafferentation compared to pre-deafferentation. The mean reduction of wave I is 0.02 ms (1 s.d.=0.16), wave III is 0.26 ms (1 s.d.=0.16), and wave V is 0.41 ms (1 s.d.=0.16). As a result, the mean interpeak intervals reduced to 1.8, 1.8 and 3.6 ms for I-III, III-V and I-V, respectively. The amplitude of each wave appears similar across all time points. Figure 2 shows box and whisker plots summarising group data for ABR latency and amplitudes. A consistent reduction in latency is apparent, and a repeated-measures ANOVA revealed a statistically significant effect of deafferentation on latency of wave III ($F_{(1,9)}=104.32$, $p<0.001$) and wave V

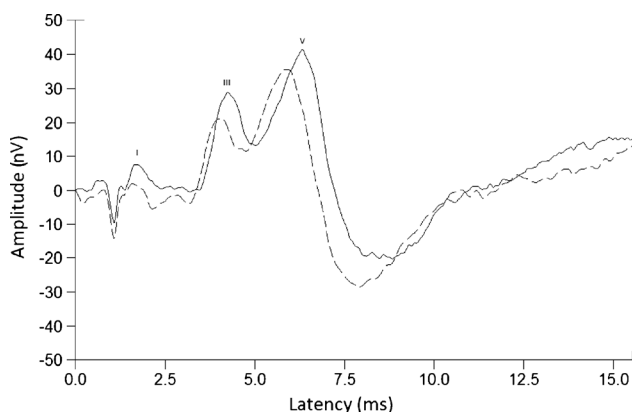


FIG. 1. Grand mean pre-labyrinthectomy (solid line) and post-labyrinthectomy (dashed line) ABR waveforms ($n=10$). The negative deflections preceding wave I are residual stimulus artefacts.

($F_{(1,9)}=58.05$, $p<0.001$). There was no statistically significant effect on amplitude for either wave III ($F_{(1,9)}=2.39$, $p=0.16$) or wave V ($F_{(1,9)}=0.79$, $p=0.40$). Data for wave I was excluded from statistical analysis to avoid loss of power through pairwise deletion, since wave I was not identifiable in all participants.

Figure 3 summarises the time course of the reduction in latency, with mean waveforms pre- and post-deafferentation plotted as a function of time. The waveform morphology is similar across all six time bins. However, reductions in ABR latency for waves III and V are apparent by the first post-deafferentation time bin. Figure 4 shows box and whisker plots summarising group data for ABR latency over time. The latencies of waves III and V appear stable across the three pre-deafferentation time bins (-3, -2, -1 h).

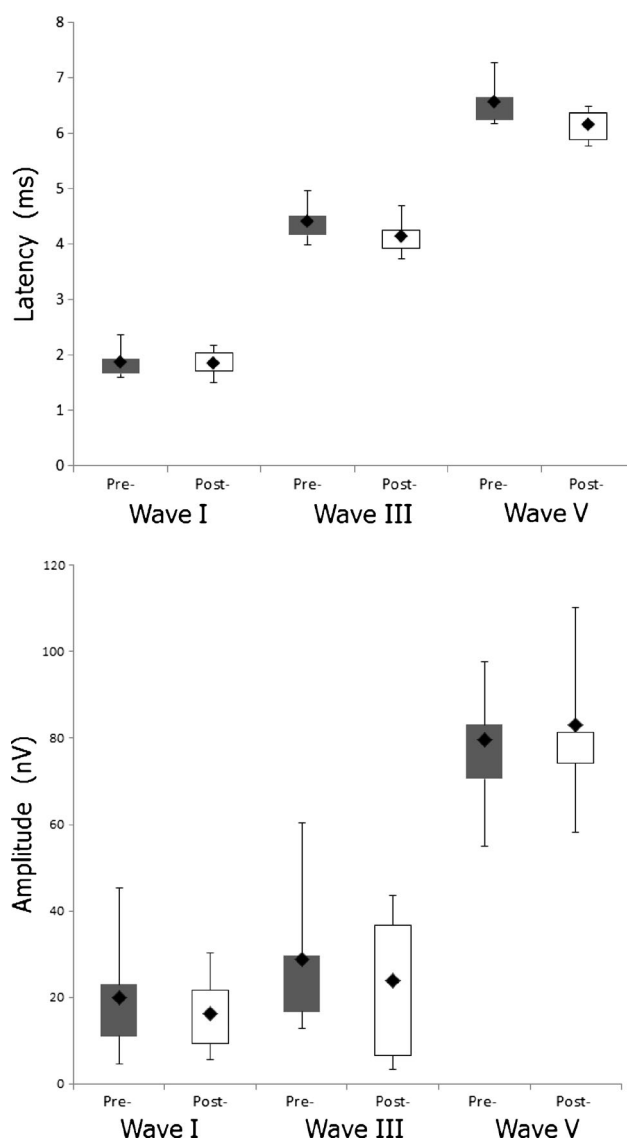


FIG. 2. Box and whisker plot showing latency data (upper panel) and amplitude data (lower panel) for waves III and V pre- (filled boxes) and post-deafferentation (open boxes).

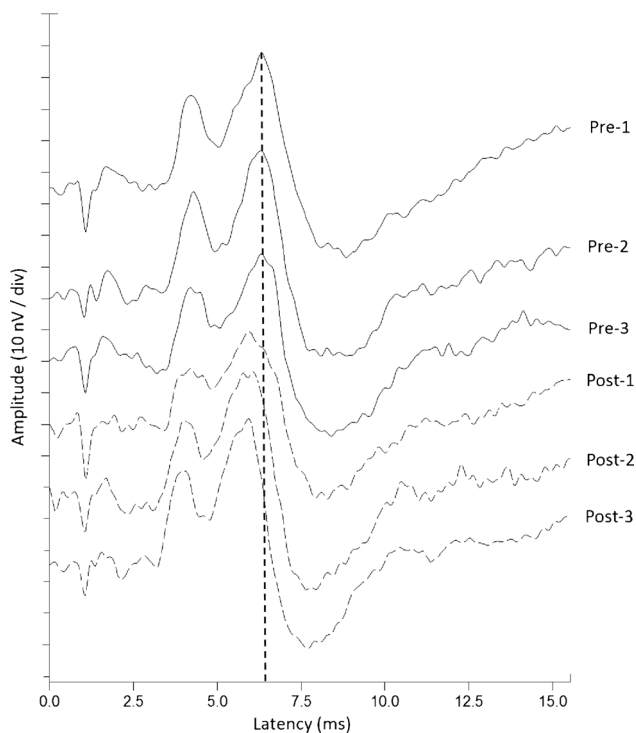


FIG. 3. Grand mean pre- and post-labyrinthectomy ABR waveforms displayed according to time bins (Pre-1, Pre-2 and Pre-3 and Post-1, Post-2 and Post-3) corresponding to -3, -1, 0, +1 and +2 h relative to deafferentation.

The reduction in mean latency of waves III and V post-deafferentation is apparent as a 'step change' by +1 h relative to deafferentation. The results of a two-factor (time [6] \times wave [2]) repeated-measures ANOVA revealed a statistically significant main effect of time ($F_{(5,45)}=18.43$, $p<0.001$), a statistically significant main effect of wave ($F_{(1,9)}=1707.22$, $p<0.001$) and a statistically significant interaction ($F_{(4,45)}=3.72$, $p=0.007$). Bonferroni-corrected post hoc pairwise comparisons were used to further investigate the main effect of time. The results revealed no statistically significant differences in latencies between pre-deafferentation time points, while latencies at each post-deafferentation time point were statistically significantly shorter than those prior to deafferentation. A full summary of the post hoc analysis is provided in Table 3.

FIG. 4. Box and whisker plot summarising latencies for wave I (upper panel), wave III (middle panel) and wave V (lower panel) as a function of time. Pre-deafferentation time points are shown as filled boxes (Pre-1, Pre-2 and Pre-3, corresponding to -3, -2 and -1 h relative to deafferentation) and post-deafferentation time points are shown as open boxes (Post-1, Post-2 and Post-3, corresponding to +1, +2 and +3 h relative to deafferentation).

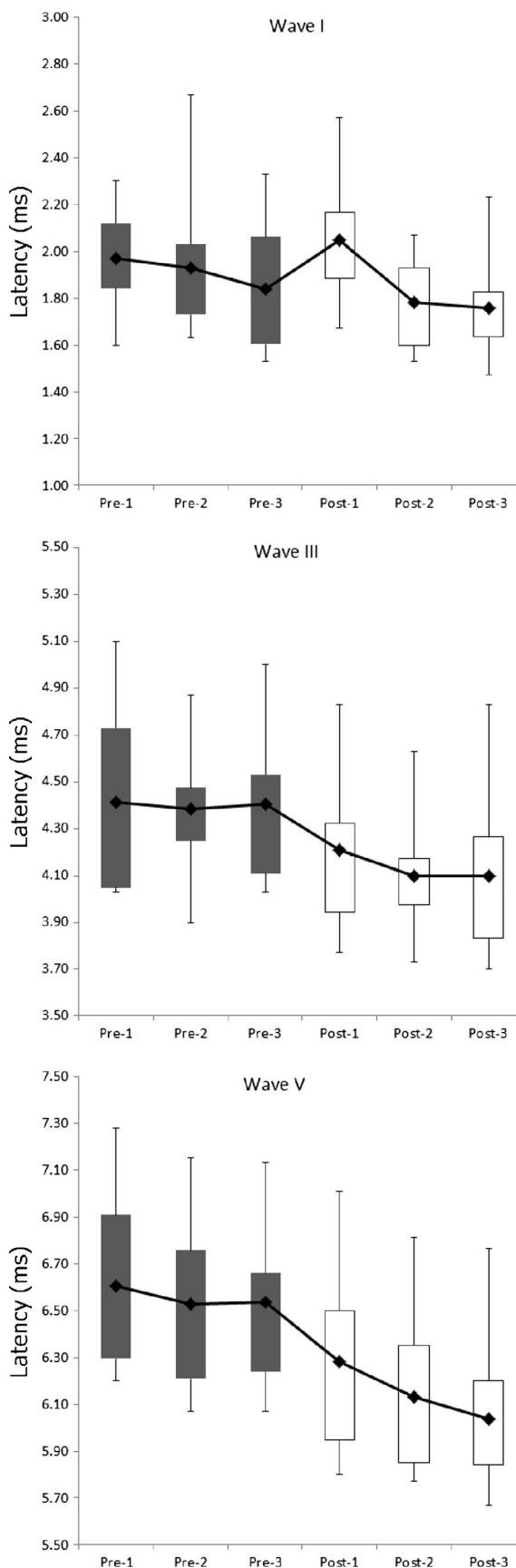


TABLE 3

Bonferroni-corrected post hoc pairwise comparison of ABR latencies pre- and post-deafferentation

Pre-1	-						
Pre-2	$p=1.00$	-					
Pre-3	$p=1.00$	$p=1.00$	-				
Post-1	$p=0.05$	$p=0.04$	$p<0.01$	-			
Post-2	$p<0.01$	$p<0.01$	$p<0.01$	$p=0.53$	-		
Post-3	$p<0.01$	$p<0.01$	$p<0.01$	$p=0.13$	$p=1.00$	-	
	Pre-1	Pre-2	Pre-3	Post-1	Post-2	Post-3	

DISCUSSION

This study compared the human ABR to stimulation of the intact ear immediately before and after surgically induced UD. This is the first study to provide evidence of a rapid (≤ 60 min) decrease in neural response time, as revealed by a decrease in mean latency of waves III and V of the ABR. The speed of change is consistent with an acute physiological mechanism, for example, unmasking of inhibition. Since most participants exhibited a partial UD in the affected ear prior to surgery, there may have already been some changes in the ABR at the baseline measure. It is therefore possible that our study has underestimated the magnitude that would have occurred if hearing had been symmetrical prior to the deafferentation.

Mechanisms Mediating Rapid Reduction in ABR Latency Post-UD

The latency of the ABR is influenced by three factors: (i) the time taken for an acoustic signal to travel through air, outer and middle ear structures and be transduced into a bioelectrical signal in the cochlea; (ii) the synaptic delay between inner hair cells in the cochlea and the auditory nerve; and (iii) the efficiency with which the signal is conducted along synchronised neurons and across synapses in the central auditory pathway (Burkard and Don 2007). Since deafferentation of one ear is unlikely to directly affect the first two factors influencing an ABR via the intact ear, the findings suggest that there is an acute increase in the efficiency and/or population of central neurons and synapses. This is consistent with the observed changes relating initially to wave III in an earlier study of deafferentation-induced neural hyperactivity (Gu et al. 2012). A possible explanation for increased efficiency of conduction is disinhibition of the intact ear and/or rapid expression of neurotransmitters, or their post-synaptic receptors, via activity-dependent intracellular signalling pathways in binaurally sensitive neurons (Moore and King 2004). Both the presence and timing of changes in the human ABR therefore resemble earlier findings in guinea pigs (Popelar et al.

(1994) and ferrets (Mossop et al. 2000). In addition to functional changes in neurons acting to decrease neural conduction time, there are other physiological mechanisms that could potentially produce a similar effect. For example, it has long been known that the presence of a unilateral acoustic neuroma can, in certain circumstances, affect the ABR to stimulation of the opposite, intact, ear. The typical effect is a decrease in amplitudes of waves III and V along with an increase in latency and a change in the overall wave morphology (Selters and Brackmann 1977; Moffat et al. 1989; Deans et al. 1990; Grabel et al. 1991). The interpretation of this effect is related to mechanical compression and/or distortion of the brainstem and the corresponding neural generators responsive to stimulation of the healthy ear. Removal of the tumour via surgery (either with or without hearing preservation) relieves the mechanical compression and leads to a renormalisation of the ABR to stimulation of the intact ear, thus producing a similar pattern of decreased latencies shown in the present study. However, there are a number of reasons to conclude that this is an unlikely explanation for the present findings. First, brainstem compression leading to measurable abnormalities in the ABR after stimulation of the non-tumour ear is rare for tumours less than 2 cm in diameter (Moffat et al. 1989). In the present study, the mean tumour size was 1.3-cm diameter and no participant had a tumour larger than 2-cm diameter. Second, brainstem compression leads to normal latency and amplitude of wave I but abnormally prolonged latencies and reduced amplitudes of waves III and V, which then return to normal after the tumour is removed. In the present study, wave III and V latencies and amplitudes fell within the normal range prior to deafferentation. Third, the changes in ABR reported in the present study commenced at the time of deafferentation, not the point of tumour removal (which occurs later in the surgical procedure).

Neural conduction, and ABR latency, is also influenced by body temperature (Legatt 2002). An increase in body temperature leads to an increase in neural conduction speed and a reduction in ABR latency (Stockard et al. 1978; Markand et al. 1987).

Therefore, it is important to account for any change in temperature in serially recorded ABR data. In the present study, there was an increase in core body temperature of 0.2 °C between the start of surgery and the labyrinthectomy, as a result of active warming via a heat blanket used to prevent hypothermia (Torossian 2008). There are a number of reasons why a change in core body temperature could not explain the sudden step change in latency. First, the increase in body temperature of around 0.2 °C will result in a negligible change in latency (Bridger and Graham 1985). Second, a gradual increase in temperature over the course of surgery would not explain the step change in latency that occurred at the point of deafferentation. Third, while core body temperature increased marginally, the temperature in the vicinity of the brainstem is more likely to have reduced due its exposure to the environment during surgery.

In contrast to changes in latency, the amplitude of the ABR was not found to change after deafferentation. The amplitude of the ABR reflects the number of phase-locked neurons that respond to a sound. Therefore, an increase in the overall response of the brainstem to stimulation of the intact ear post-UD would be expected to produce an increase in ABR amplitude via a greater number of neurons contributing to the signal. An increase in cortical evoked response amplitude have been reported previously (Ponton et al. 2001; Maslin et al. 2013a, b). Studies involving the ABR often avoid reporting amplitude because of variability, even when measured under the same stimulus and recording conditions (Burkard and Don 2007). The variability occurs because the ABR amplitude is known to be influenced by factors which may vary over the course of a recording session including myogenic noise and external noise (electrical and/or acoustic) and fixed factors for each individual (but variable between individuals) such as hearing sensitivity, skull thickness, size and orientations of the neural generators. Although the repeated-measures design of the present study should control for fixed factors, the amount of residual noise contributing to each average response is still likely to have varied due to the aforementioned non-fixed factors. This would act to reduce the effect size for any changes in ABR amplitude. Future studies may benefit from quantitative measures of residual noise so that signal to noise ratio across conditions could be matched, allowing a fair comparison of amplitude (Elberling and Don 1984). Nevertheless, increases in ABR amplitude, assumed to be triggered by deafferentation, have been reported elsewhere (e.g. Schaette and McAlpine 2011; Gu et al. 2012).

Although the findings from animal studies support a reduction in latency after deafferentation, an

apparent reduction in latency could also occur if a change in waveform morphology resulted in a re-shaping of the peak. Whilst we cannot rule out this possibility, it would seem unlikely given that the peaks were clearly defined and there is little difference in waveform morphology pre- and post-labyrinthectomy.

Tinnitus, the perception of sound in the absence of an external source, is a common hearing disorder, affecting around 10 % of adults (Davis and Rafaie 2000). Although tinnitus and hyperacusis were not specifically investigated as part of the present study, the epidemiology of tinnitus in acoustic neuroma patients is well documented. Around 50 % of patients do not have tinnitus before surgery, but of these cases, around 50 % will develop tinnitus post-surgery (Baguley et al. 1992; Fahy et al. 2002). There is a consensus that chronic tinnitus, and hyperacusis (and oversensitivity to the loudness of sound), is related to maladaptive increases in neural activity within the auditory system triggered by partial deafferentation (Baguley 2002; Norena and Eggermont 2003; Kaltenbach 2011; Zeng 2013). Although no causal interventions for tinnitus currently exist, a clearer understanding of the mechanisms of plasticity leading to the increased neural activity might lead to the development of a causal intervention.

CONCLUSIONS

The present study is the first to demonstrate the following: (i) sub-cortical plasticity and (ii) rapid onset following UD in adult humans. In particular, there is a reliable increase in neural conduction speed across participants of around 6 %. The rapid increase in neural conduction at the point of deafferentation is consistent with acute, physiological mechanisms shown in animal research. Future studies are needed to investigate neural changes that take place over a longer time course, to clarify changes in amplitude as well as latency of the ABR and to investigate the perceptual consequences of these physiological changes. Participants due to undergo surgically induced UD represent a unique opportunity to establish the role of maladaptive plasticity in tinnitus and hyperacusis and to objectively quantify symptoms, both essential steps towards development of urgently needed causal interventions.

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