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The Role of the Salience Network in Processing Lexical and Nonlexical Stimuli in Cochlear Implant Users: An ALE Meta-Analysis of PET Studies

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Abstract: Previous positron emission tomography (PET) studies have shown that various cortical areas are activated to process speech signal in cochlear implant (CI) users. Nonetheless, differences in task dimension among studies and low statistical power preclude from understanding sound processing mechanism in CI users. Hence, we performed activation likelihood estimation meta-analysis of PET studies in CI users and normal hearing (NH) controls to compare the two groups. Eight studies (58 CI subjects/92 peak coordinates; 45 NH subjects/40 peak coordinates) were included and analyzed, retrieving areas significantly activated by lexical and nonlexical stimuli. For lexical and nonlexical stimuli, both groups showed activations in the components of the dual-stream model such as bilateral superior temporal gyrus/sulcus, middle temporal gyrus, left posterior inferior frontal gyrus, and left insula. However, CI users displayed additional unique activation patterns by lexical and nonlexical stimuli. That is, for the lexical stimuli, significant activations were observed in areas comprising salience network (SN), also known as the intrinsic alertness network, such as the left dorsal anterior cingulate cortex (dACC), left insula, and right supplementary motor area in the CI user group. Also, for the

Contract grant sponsor: The National Research Foundation of Korea (NRF) grant of the Korea government (MSIP); Contract grant number: 2014002619

The authors have no conflict of interest.

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Received for publication 27 June 2014; Revised 8 December 2014; Accepted 13 January 2015.

DOI: 10.1002/hbm.22750

Published online 00 Month 2015 in Wiley Online Library (wileyonlinelibrary.com).

nonlexical stimuli, CI users activated areas comprising SN such as the right insula and left dACC. Previous episodic observations on lexical stimuli processing using the dual auditory stream in CI users were reconfirmed in this study. However, this study also suggests that dual-stream auditory processing in CI users may need supports from the SN. In other words, CI users need to pay extra attention to cope with degraded auditory signal provided by the implant. *Hum Brain Mapp* 00:000–000, 2015. © 2015 Wiley Periodicals, Inc.

Key words: cochlear implant; positron emission tomography; brain; meta-analysis

INTRODUCTION

Cochlear implantation (CI), surgical insertion of electrodes into the cochlea, is so far the only available medical technique that can successfully replace a deficient sensory modality in humans. CI has been established as a standard treatment option for subjects with profound hearing loss, and thus more than 200,000 recipients including 80,000 children have been rehabilitated with CI [Kral and O'Donoghue, 2010; Zeitler et al., 2011]. From neuroscientists' viewpoint, CI also provides a unique opportunity to study cortical change associated with profound sensorineural hearing loss and restoration of the auditory modality [Giraud et al., 2001; Lazard et al., 2014; Song et al., 2013b].

However, even for a proficient CI user, poorly represented temporal fine structure and limited spectral cues delivered by the implant, yield impoverished input to the auditory cortex when compared with normal acoustic stimulation [Kral and O'Donoghue, 2010]. Thus, CI recipients show various performances. This large range of variability in post-CI outcomes has long been investigated. Preoperative hypometabolism in the auditory cortex [Lee et al., 2001, 2007a] and postoperative hypermetabolism in the visual cortex [Strelnikov et al., 2013] have been suggested to be positively correlated with speech performance.

In this regard, researchers have been investigating brain activation patterns in deaf subjects with CI using functional imaging techniques, mostly positron emission tomography (PET). PET is optimal functional neuroimaging tool for CI users [Song et al., 2014b] as compared with other methodologies such as functional magnetic resonance imaging, magneto- or electroencephalography [Song et al., 2013a, 2014a, 2015]. In the early era of PET studies on CI users, most studies adopted regions of interest (ROIs) such as primary/secondary auditory cortices (A1/A2), Broca's/Wernicke's areas for statistical analysis and found relative increase of regional cerebral blood flow (rCBF) of these areas for sound stimuli as in normal hearing (NH) controls [Naito et al., 1995; Okazawa et al., 1996]. However, progress in imaging analysis techniques and accumulation of knowledge that various nonauditory brain regions other than aforementioned ROIs are activated during sound perception and interpretation in NH people

[Hickok and Poeppel, 2007; Hickok et al., 2011; Rauchschecker, 2011], studies on CI subjects have implemented data-driven whole brain approach. Thus, various nonauditory multisensory brain areas have been revealed to be activated by both lexical and nonlexical stimuli [Giraud and Truy, 2002; Giraud et al., 2001].

Hitherto individual PET studies in CI subjects vary in tasks (i.e., phoneme, word, sentence, time-reversed sentence, foreign language, environmental sound, and white noise) and are limited by statistical power and sensitivity due to small number of enrolled subjects. As an option to overcome these limitations, function-location meta-analysis permits to retrieve the most consistent activation areas as well as to compare results across different task dimensions in a standardized fashion [Laird et al., 2005].

Hence, we performed a meta-analysis of PET studies on CI subjects by use of a coordinate-based technique (activation likelihood estimation; ALE) [Song et al., 2012; Turkeltaub et al., 2002] to get a better understanding of the characteristic features of cortical activation patterns for both lexical and nonlexical auditory stimuli processing in CI relative to NH subjects.

MATERIALS AND METHODS

Selection Criteria and Included Studies

To identify all studies available, multiple PubMed searches on PET studies on CI according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [Moher et al., 2009] were performed. Keywords used in the search were: "positron emission tomography" and "cochlear implant" with activated limits: article types other than review; human species; English language.

The inclusion criteria were that studies

1. Published in a peer-reviewed journal,
2. Used a task involving passive hearing of auditory-only stimulus,
3. Enrolled adult CI subjects (>18 years) who had bilateral postlingual profound hearing loss
4. Enrolled CI subjects who were implanted unilaterally,

5. Enrolled CI subjects who showed good performance enough to regain speech performance in everyday life (scores for word discrimination >60% or for sentence comprehension >70%) to reduce performance-related confound. Only two of the included studies included “poor performers,”
6. Based on a data-driven whole-brain approach for meta-analysis. Studies based on selected ROIs were excluded,
7. Were reported in standard stereotaxic spaces such as Montreal Neurological Institute (MNI) [Collins et al., 1994] or Talairach and Tournoux space [Talairach and Tournoux, 1988]
8. Were driven by categorical contrasts rather than correlation analyses, and
9. Reported a t -value ≥ 3 or a Z -score ≥ 2.33 to ensure comparable specificity [Friebel et al., 2011].

Of 63 initially retrieved studies, eight met our inclusion criteria [Coez et al., 2008; Giraud and Truy, 2002; Giraud et al., 2001; Mortensen et al., 2006; Naito et al., 2000; Nishimura et al., 2000; Song et al., in press; Wong et al., 1999]. Of these eight studies, six [Coez et al., 2008; Giraud and Truy, 2002; Giraud et al., 2001; Naito et al., 2000; Song et al., in press; Wong et al., 1999] included NH controls that underwent the same PET experiment paradigms, and thus these six studies were used for ALE meta-analyses on the cortical activation pattern of sound processing in NH controls. In total, 58 CI subjects with a total of 92 peak coordinates (Table I) and 45 NH subjects with a total of 40 peak coordinates (Table II) were included for the current meta-analysis. The literature search, selection, and compilation of coordinates for the contrast were performed independently by two investigators (J-J.S and S.V), and the meta-analysis was performed after confirming that the selected articles for final inclusion were concordant between the two.

Meta-Analysis Algorithm

To determine the concurrence in reported coordinates across the included studies, we conducted ALE meta-analyses for three contrasts, namely “lexical stimuli–baseline,” “nonlexical stimuli–baseline,” and “lexical stimuli–nonlexical stimuli,” both in CI users and NH controls using the software Brainmap GingerALE (<http://brainmap.org/ale/index.html>) desktop application ver. 2.3.1. Because only one study [Mortensen et al., 2006] provided results from the contrast “nonlexical stimuli–lexical stimuli,” we could not conduct ALE meta-analysis for this contrast. The method we used for our meta-analysis is the latest revised version of the ALE approach [Turkeltaub et al., 2012] for coordinate-based meta-analysis of neuroimaging results [Eickhoff et al., 2009; Laird et al., 2005; Turkeltaub et al., 2002]. Turkeltaub’s nonadditive ALE algorithm minimizes both within-experiment and within-

group effects, and thus, optimizes the degree to which ALE values represent concordance of statistically significant findings across independent studies included [Eickhoff et al., 2012; Turkeltaub et al., 2012]. For each analysis, we used Talairach and Tournoux’s coordinate space [Talairach and Tournoux, 1988] and more conservative gray matter mask in the GingerALE preferences menu. The FWHM values were subject-based [Eickhoff et al., 2009], with no additional FWHM.

The input for the first meta-analysis consisted of the coordinates of brain regions that were activated in response to lexical stimuli (words or sentences) compared to baseline images. For the first analysis, studies 1, 2, 3, 6, and 8 (40 CI subjects with 40 foci) were adopted for the CI user group and studies 1, 2, and 6 (27 NH controls with 25 foci) were adopted for the NH control group (Table III). For the second analysis, coordinates that were significantly modulated by nonlexical stimuli such as white noise or nonvoice sounds as compared with baseline were analyzed. For the second analysis, studies 1, 3, 6, and 7 (30 CI subjects with 20 foci) were used for the CI user group and studies 1, 2, and 5 (23 NH controls with 18 foci) were used for the NH control group (Table IV). The third meta-analysis included coordinates of brain regions that were activated more by lexical stimuli than by nonlexical stimuli. For this third analysis, studies 1, 4, 5, and 6 (24 CI subjects with 20 foci) were used for the CI user group and studies 1, 3, 4, and 5 (23 NH controls with 9 foci) were used for the NH control group (Table V).

For the resulting ALE map, a statistical threshold of $P < 0.05$, false discovery rate (FDR)-corrected for multiple comparisons [Laird et al., 2005] and a minimum cluster size of 50 mm^3 were adopted. Statistically significant voxels obtained by the current ALE meta-analyses represent the concordance of the investigated effect across the studies. ALE results were then overlaid onto a standardized individual anatomical T1-template (<http://www.brainmap.org/ale/Colin1.1.nii>) and cluster centers were anatomically delineated using MRICron software (<http://www.sph.sc.edu/comd/rorden/mricron/>) [Rorden et al., 2007]. To describe correct location of each cluster center, all the peak coordinates and their designated locations both as brain regions and Brodmann areas (BAs) were reconfirmed using Talairach and Tournoux’s atlas [Talairach and Tournoux, 1988].

RESULTS

Significant ALE Clusters for the Contrast (Lexical Stimuli–Resting State)

The results of the first analysis, contrasting lexical stimuli and baseline resting state both in CI users and NH controls are summarized in Figure 1 and Table III. For the lexical stimuli condition, both the CI user- and NH control groups revealed activation of bilateral primary auditory-

TABLE I. Patients included in the ALE meta-analyses

Study number	Author	Year	Patients	CI side	Handedness	Contrast	Side	Anatomic Site							
1	Wong	1999	5	5R	R	Sentence–baseline	R	STG/MTG/TTG							
							L	STG/MTG							
							R	STG							
						Word–baseline	L	STG/MTG							
							L	MTG							
							L	STG							
						Time–reversed sentence–baseline	R	Cerebellum							
							R	MTG							
							L	Temporal lobe/STG							
2	Nishimura	2000	6	NA	R	Sentence–time–reversed sentence	R	MTG							
							L	Temporal lobe/STG							
3	Naito	2000	12	6R, 6L	R	Word–baseline	R	STG/MTG							
							R	SMA							
							L	STG/MTG							
						Sentence–baseline	L	IFG, post							
							L	HG							
							L	ACC							
						White noise–baseline	R	SMG							
							R	STG/MTG							
							R	Thalamus/putamen							
							R	Cerebellum							
							R	IFG, post							
							R	SMA							
							L	HG							
							L	STG/MTG							
							L	IFG, post							
4	Giraud	2001	6	4R, 2L	R	Speech–environmental	L	ITG, post							
							5	Giraud	2002	6	4R, 2L	NA	French–Norwegian	R	TOP junction
														R	FG
R	OG														
6	Mortensen	2006	7	2R, 5L	NA	White noise–baseline	L	SPC							
							L	ITG, post							
							L	PFC, inf							
6	Mortensen	2006	7	2R, 5L	NA	Word–baseline	R	STG							
							L	STG							
							R	STG, ant/post							
						Speech–baseline	L	STG							
							L	PFC, inf							
							R	STG							
						Speech–white noise	R	cerebellum							
							L	STG							
							L	PreCG/SFG							
						Baseline–white noise	R	STG, ant/post							
							R	cerebellum							
							L	temporal pole							
						Baseline–speech	L	STG, ant/post							
							L	PFC, inf							
							R	Cerebellum							
white noise –speech	L	Cerebellum													
	R	MFG													
	R	Cuneus/ precuneus													
	R	Cerebellum													
	L	Cerebellum													
	L	Cuneus													
							R	MTG							
							R	Precuneus							
							R	PHG							
							L	Lingual gyrus							

TABLE I. (continued).

Study number	Author	Year	Patients	CI side	Handedness	Contrast	Side	Anatomic Site
7	Coez	2008	6	2R, 4L	R	nonvoice –baseline	R	STS, middle/post
							R	Distal FG
							L	STS, ant/middle/post
						Voice–nonvoice	R	STS, middle/post
							R	STG
8	Song	2014	10	6R, 4L	R	Word–baseline	L	STS, ant/middle
							R	STG
							L	MTG
							L	STG
							L	Temporal pole

CI, cochlear implant; R, right; L, left; NA, not available; STG, superior temporal gyrus; MTG, middle temporal gyrus; TTG, transverse temporal gyrus; SMA, supplementary motor area; HG, hippocampal gyrus; ACC, anterior cingulate cortex; SMG, supramarginal gyrus; IFG, inferior frontal gyrus; post, posterior; ITG, inferior temporal gyrus; TOP, temporo-occipito-parietal; FG, fusiform gyrus; OG, occipital gyrus; SPC, superior parietal cortex; ant, anterior; PFC, prefrontal cortex; inf, inferior; PreCG, precentral gyrus; SFG, superior frontal gyrus; MFG, middle frontal gyrus; PHG, parahippocampal gyrus; STS, superior temporal sulcus; FG, frontal gyrus.

TABLE II. Normal controls included in the ALE meta-analyses

Study number	Author	Year	Controls	Handedness	Contrast	Side	Anatomic Site
1	Wong	1999	5	R	Word–baseline	R	STG/MTG
						L	STG
					Sentence–baseline	R	MTG
						L	STG/MTG
						L	IFG
2	Naito	2000	12	R	Sentence–baseline	R	SMG
						R	STG/MTG
						L	STG
						L	IFG, post
						L	HG
					White noise–baseline	L	Caudate nucleus
						R	TTG
						R	Putamen
						R	HG
						L	ITG
3	Giraud	2001	6	R	Speech–environmental	L	Wernickes' area
						L	ACC
4	Giraud	2002	6	NA	French–Norwegian	L	ITG, post
						L	SPC
						R	OG
5	Coez	2008	6	R	Nonvoice–baseline	R	STS, ant/post
						R	Uncus
						L	STS, ant/post
					Voice–nonvoice	R	STS, middle/post
						L	STS, middle/post
6	Song	2014	10	R	Word–baseline	R	STG
						R	MTG
						R	Thalamus
						L	STG
						L	MTG
						L	Thalamus

CI, cochlear implant; R, right; L, left; NA, not available; STG, superior temporal gyrus; MTG, middle temporal gyrus; IFG, inferior frontal gyrus; SMG, supramarginal gyrus; post, posterior; HG, hippocampal gyrus; TTG, transverse temporal gyrus; ITG, inferior temporal gyrus; ACC, anterior cingulate cortex; SPC, superior parietal cortex; OG, occipital gyrus; ant, anterior.

TABLE III. Summary of the spatial location and extent of ALE values for the contrast (lexical stimuli–baseline) in the cochlear implant patients and normal hearing controls (FDR corrected $P < .05$, voxel size > 50)

Side	BA	Region	Volume (mm ³)	Weighted Center			Max ALE Value
				<i>x</i>	<i>y</i>	<i>z</i>	
<i>Cochlear implant patients (contributed studies: studies 1, 2, 3, 6, and 8 of Table I)</i>							
L	22	STG/STS	3,528	-57	-25	3	0.014
L	22	MTG	i.above				0.013
L	22	STG/STS	i.above				0.010
R	22	STG/STS	1,080	57	-24	4	0.012
R	38	STG	1,008	52	1	-7	0.011
L	22	STG	368	-48	-6	-4	0.009
R		MTG	112	50	-31	0	0.007
L	38	STG	104	-53	5	-7	0.007
L	21	MTG	80	-59	-3	-3	0.007
L	28	PHG	56	-30	6	-20	0.007
L	13	Insula	56	-44	10	12	0.007
L	32	ACC	56	-6	16	40	0.007
R	6	SMA	56	4	8	52	0.007
<i>Normal hearing controls (contributed studies: studies 1, 2, and 6 of Table II)</i>							
R	21	MTG	552	57	-8	-5	0.011
R	22	STG/STS	368	58	-25	1	0.009
L	22	STG	200	-49	-10	0	0.008
L	22	MTG	72	-50	-36	4	0.007
R	38	STG	64	48	2	-8	0.007
L		MTG	64	-65	-26	0	0.007
L	13	Insula	56	-38	-20	-8	0.007
L	44	pIFG	56	-42	14	8	0.007
L		Caudate body	56	-14	20	8	0.007
L		Caudate tail	56	-26	-34	12	0.007

FDR, false detection rate; L, left; R, right; BA, Brodmann area; STG, superior temporal gyrus; STS, superior temporal sulcus; MTG, middle temporal gyrus; ACC, anterior cingulate cortex; SMA, supplementary motor area; pIFG, posterior inferior frontal gyrus.

and secondary auditory cortices (A1 and A2), namely superior- and middle temporal gyri (STG and MTG, BAs 21 and 22) and superior temporal sulcus (STS). In CI users, significant activations for lexical stimuli were observed in the left insula (BA 13), left dorsal anterior cingulate cortex (dACC, BA 32), left parahippocampal gyrus (PHG, BA 28), and the right supplementary motor area (SMA, BA 6; Fig. 1, upper panels). In contrast, the NH group displayed increased rCBF in the left insula (BA 13), left posterior inferior frontal gyrus (pIFG, BA 44), and the caudate body and tail (Fig. 1, lower panels).

Significant ALE Clusters for the Contrast (Nonlexical Stimuli–Resting State)

By the second analysis contrasting nonlexical sound stimuli and silent baseline, the CI user group showed significant increases in rCBF in the left A2 (BA 22) and the NH control group in the right A2 (BA 21; Fig. 2 and Table IV). Also, both groups displayed increased rCBF in the cerebellum (the CI user group in the cerebellar culmen and vermis; the NH control group in the cerebellar cul-

men). Of note, the CI user group activated the right insula (BA 13), right thalamic ventrolateral nucleus VLN, right caudate body, and the left dACC (BA 24) under the nonlexical stimuli condition (Fig. 2, upper panels), while the NH control group revealed activations in the right caudate tail and right PHG (BA 36; Fig. 2, lower panels).

Significant ALE Clusters for the Contrast (Lexical Stimuli–Nonlexical Stimuli)

The third contrast, lexical stimuli minus nonlexical stimuli, revealed significant increases in rCBF in the bilateral A1/A2 and the fusiform gyrus in both the CI user- and NH control groups (Fig. 3 and Table V). The CI user group uniquely activated the left inferior frontal gyrus (IFG, BA 47) more under the lexical stimuli than under the nonlexical stimuli (Fig. 3, upper panels). Also, the CI users showed increased activation in the cerebellar uvula under the lexical stimuli as compared with nonlexical stimuli. In contrast, the NH controls displayed increased activation in the postcentral gyrus (PoCG, BA 5) under the lexical

TABLE IV. Summary of the spatial location and extent of ALE values for the contrast (nonlexical stimuli–baseline) in the cochlear implant patients and normal hearing controls (FDR corrected $P < .05$, voxel size > 50)

Side	BA	Region	Volume (mm ³)	Weighted Center			Max ALE Value
				<i>x</i>	<i>y</i>	<i>z</i>	
<i>Cochlear implant patients (contributed studies: studies 1, 3, 6, and 7 of Table I)</i>							
L	22	STG/STS	480	-55	-26	4	0.008
L	22	STG	248	-48	2	-5	0.007
R		Cbll culmen	160	26	-56	-24	0.007
R		Cbll culmen	152	6	-42	-20	0.007
R	13	Insula	152	34	-30	26	0.007
R		Caudate body	96	15	12	11	0.007
L	24	dACC	96	-3	4	35	0.007
L		Cbll culmen	80	-11	-42	-2	0.007
R		Putamen	80	24	4	7	0.007
R		Cbll vermis	64	1	-73	-15	0.007
R		Thalamic VLN	64	17	-15	17	0.007
<i>Normal hearing controls (contributed studies: studies 1, 2, and 5 of Table II)</i>							
R	21	STG/STS	448	55	-9	-4	0.009
L		Cbll culmen	152	-6	-48	-6	0.007
R		Caudate tail	96	31	-36	5	0.007
R		Putamen	96	15	3	10	0.007
R		Caudate tail	96	33	-44	15	0.007
R	36	PHG	80	33	-30	-12	0.007
L		Cbll culmen	80	-1	-38	-6	0.007

FDR, false detection rate; L, left; R, right; BA, Brodmann area; STG, superior temporal gyrus; STS, superior temporal sulcus; Cbll, cerebellar; dACC, dorsal anterior cingulate cortex; VLN, ventrolateral nucleus; MTG, middle temporal gyrus; FG, fusiform gyrus; PHG, parahippocampal gyrus.

TABLE V. Summary of the spatial location and extent of ALE values for the contrast (lexical stimuli–nonlexical stimuli) in the cochlear implant patients and normal hearing controls (FDR corrected $P < .05$, voxel size > 50)

Side	BA	Region	Volume (mm ³)	Weighted Center			Max ALE Value
				<i>x</i>	<i>y</i>	<i>z</i>	
<i>Cochlear implant patients (contributed studies: studies 1, 4, 5, and 6 of Table I)</i>							
R	22	STG/STS	792	60	-24	1	0.010
L	21	MTG	744	-60	-10	-3	0.007
L	22	STG/STS	176	-60	-25	2	0.006
R		Cbll uvula	80	25	-80	-24	0.005
L	38	STG	80	-38	12	-22	0.006
L	47	pIFG	80	-46	17	-4	0.005
R	22	STG	80	55	-10	-3	0.005
L	37	Fusiform G	56	-46	-46	-14	0.005
L	22	STG	56	-34	24	-14	0.005
L	37	MTG	56	-42	-58	-4	0.005
<i>Normal hearing controls (contributed studies: studies 1, 3, 4, and 5 of Table II)</i>							
L	21	MTG	160	-64	-30	-2	0.005
R	18	Fusiform G	56	22	-90	-14	0.005
L	19	ITG	56	-44	-58	-6	0.005
R	21	STS	56	62	-30	0	0.005
L	22	STS	56	-62	-14	0	0.005
L	5	PoCG	56	-34	-40	58	0.005

FDR, false detection rate; L, left; R, right; BA, Brodmann area; STG, superior temporal gyrus; STS, superior temporal sulcus; pIFG, posterior inferior frontal gyrus; MTG, middle temporal gyrus; Cbll, cerebellar; ITG, inferior temporal gyrus; FG, fusiform gyrus; PoCG, postcentral gyrus.

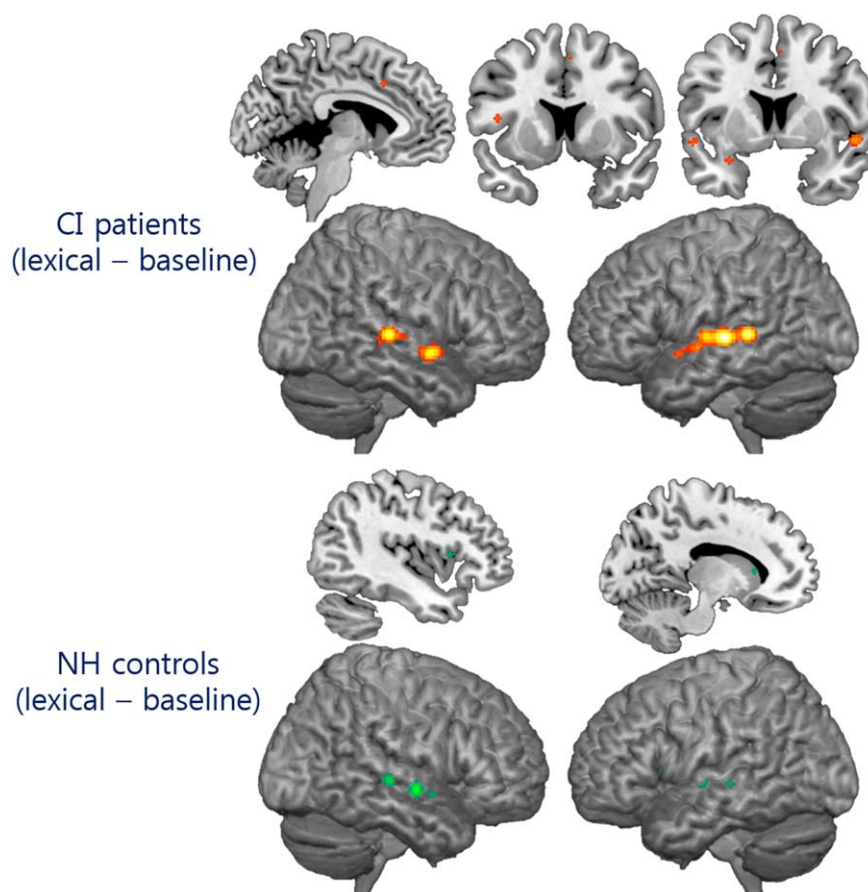


Figure 1.

Main activation effects in cochlear implant (CI) subjects (upper panel) and normal hearing (NH) controls (lower panel) under lexical stimuli (FDR corrected $P < 0.05$, $k > 50$ voxels). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

stimuli as compared with nonlexical stimuli (Fig. 3, lower panels).

DISCUSSION

To understand the mechanism of speech processing in NH individuals, researchers have endeavored to develop integrative models for speech perception. The dual-stream model [Hickok and Poeppel, 2007; Hickok et al., 2011], a representative model of speech processing, holds that early stages of speech perception occurs in auditory regions consisting of the dorsal STG and STS bilaterally and then diverges into two broad streams: the ventral stream, a bilaterally organized structure consisting of MTG and inferior temporal sulcus that directly processes speech signals for comprehension, and the dorsal stream, a strongly left-hemisphere dominant structure consisting of parietal-temporal junction, posterior IFG, premotor cortex, and anterior

insula that maps acoustic speech signals to frontal lobe articulatory networks [Hickok and Poeppel, 2000, 2004, 2007].

As in NH subjects, researchers have been investigating the cortical organization of speech processing in CI users. Parts of cortical areas that were suggested to be involved in the dual-stream model in NH subjects also showed increased activity by auditory stimuli in CI users [Giraud et al., 2000], visually evoked phonological and environmental sound representations [Lazard et al., 2013], or speechreading [Lee et al., 2007b]. Also, an fMRI study in postlingual deafened subjects using rhyming task on written regular words has indicated that subjects who rely on a dorsal phonological route will become good CI performers while ventral temporo-frontal route-dependent subjects will become poor CI performers [Lazard et al., 2010].

However, these observations in CI users do not preclude the possibility of different speech processing strategy,

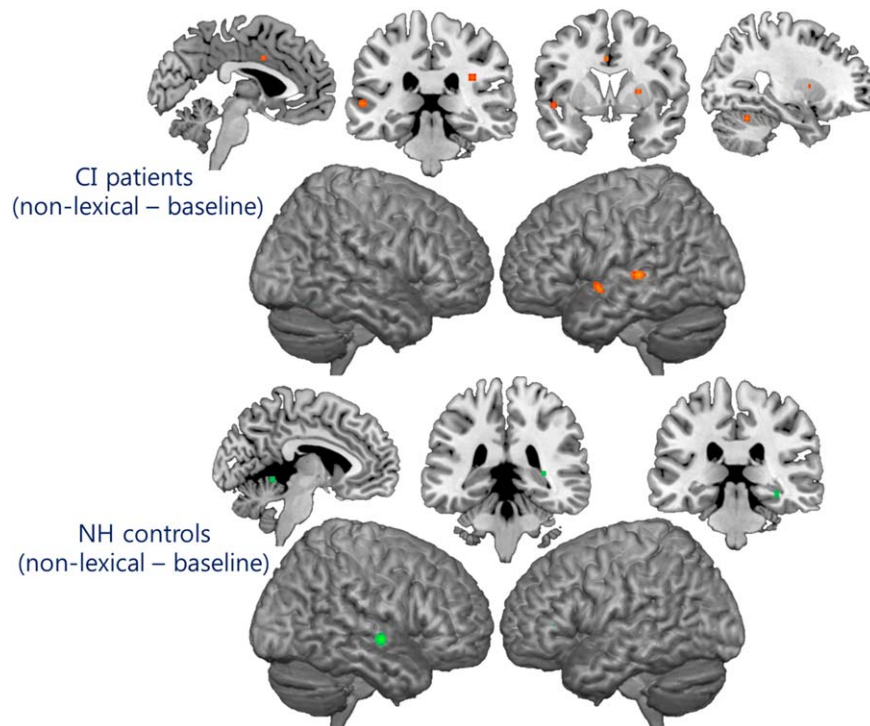


Figure 2.

Main activation effects in CI subjects (upper panel) and NH controls (lower panel) under lexical stimuli (FDR corrected $P < 0.05$, $k > 50$ voxels). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

especially considering deafness-induced plastic changes and intrinsically distorted and impoverished auditory inputs provided by the CI [Lazard et al., 2012]. Indeed, by

performing the current meta-analysis, we corroborated different speech and nonspeech sound processing patterns in CI users.

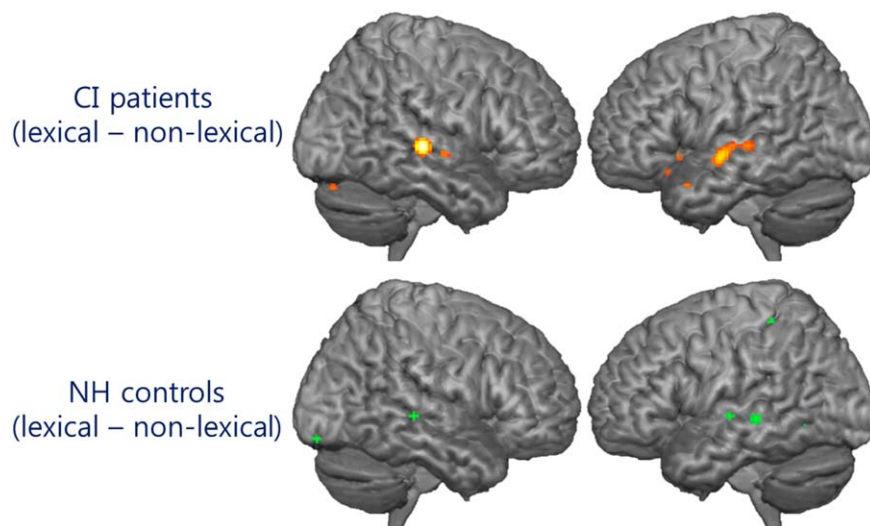


Figure 3.

Main activation effects in CI subjects (upper panel) and NH controls (lower panel) for the contrast “lexical stimuli–nonlexical stimuli (FDR corrected $P < 0.05$, $k > 50$ voxels). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Activation of the Dual Streams for Speech Processing in CI Users as in NH Controls

For lexical stimuli, the NH control group showed increased rCBF in areas comprising the phonological network (bilateral STS), spectrotemporal analysis (STG), articulatory network (left insula and pIFG), and lexical interface (MTG) of the dual-stream speech processing system [Hickok and Poeppel, 2004, 2007] (Fig. 1 and Table III). For the contrast “lexical stimuli–nonlexical stimuli,” NH controls displayed increased activations in areas comprising the phonological network (bilateral STS), lexical interface (MTG), and sensorimotor interface (PoCG; Fig. 3 and Table V). The NH control group in the current meta-analysis, therefore, used both ventral and dorsal language processing routes for lexical stimuli.

The CI user group also showed increased rCBF in areas comprising the phonological network (bilateral STS), spectrotemporal analysis (STG), articulatory network (left insula), and lexical interface (MTG) of the dual-stream speech processing system for lexical stimuli (Fig. 1 and Table III). Also, the CI user group showed increased activations in areas at the phonological network (bilateral STS), spectrotemporal analysis (STG), articulatory network (left pIFG), lexical interface (left posterior MTG), and combinatorial network (left anterior MTG) for the contrast “lexical stimuli–nonlexical stimuli” (Fig. 3 and Table V). By observing these relative activations, utilization of the dual-stream speech processing system for lexical stimuli in CI users was reconfirmed, and these results are in line with previous reports [Giraud and Lee, 2007; Lazard et al., 2010; Lee et al., 2007a]. In summary, these episodic reports on the utilization of dual auditory stream for speech processing in CI users were reconfirmed in this study in a meta-analytic level.

Meanwhile, nonlexical stimuli increased cerebellar areas both in the CI user group and NH group (Fig. 2 and Table IV). As the cerebellum may be involved in purely sensory auditory processing [Petacchi et al., 2005], cerebellar activations may designate similar sound processing strategies for nonlexical stimuli in both groups.

One important discrepancy between the current and previous studies should be addressed. Previous reports have suggested an important role of the right posterior temporal gyrus in processing nonspeech sound not only in NH subjects [Halpern and Zatorre, 1999] but also in CI users [Lazard et al., 2011]. In contrast, the current meta-analysis found right posterior temporal activation only in the NH control group, not in the CI user group. This may be attributed to the differences in task dimension (sound imagery vs. real sound presentation) or sample size-related differences in statistical power. Future studies should be performed to reevaluate this discrepancy.

CI Users Need Attention Control to Process Speech Sound: Activation of Salience Network for Lexical Stimuli

Adding to the utilization of the dual-stream speech processing system, CI users demonstrated unique activation patterns that were not observed in NH controls both for lexical and nonlexical stimuli.

For the lexical stimuli, significant activations were observed in areas at the left dACC, left insula, and right SMA in the CI user group. These three areas are left-sided components of previously reported bilateral salience network (SN) [Bonnelle et al., 2012; Seeley et al., 2007], a network activated when behaviorally relevant information is processed [Seeley et al., 2007; Sridharan et al., 2008]. The SN operates to control dynamic changes of activity in other cortical networks [Sridharan et al., 2008], and the role of the SN as a mediator of the function of other networks seems to be most evident when a rapid change in behavior is required. In particular, the integrity of the SN is crucial for the efficient regulation of activity in the default mode network [Bonnelle et al., 2012] that is important for efficient behavioral performance. Considering impoverished auditory input processed by the CI, the activation of the SN for lexical stimuli may indicate that salience is attached to the stimuli, both top down, that is, behaviorally relevant [Seeley et al., 2007], and bottom up, that is, distinctive [Fecteau and Munoz, 2006; Serences and Yantis, 2006], to process distorted speech cues in CI users. In NH people listening to acoustically degraded words using vocoder, the activity in the dACC was mainly affected only when there was a behavioral task involved [Obleser and Weisz, 2012]. This is in line with the results of the current study in that CI users in the included studies were exposed to degraded lexical auditory input, and of five studies used for the contrast “lexical stimuli–baseline,” four used tasks such as button-pressing [Wong et al., 1999], mouse-clicking [Song et al., in press], or answering to questions after each measurement [Mortensen et al., 2006; Naito et al., 2000] to maintain attention level of the participants. The activation of the SN may also explain markedly broad activation of the A1/A2 in CI users for lexical stimuli as compared with NH controls (Fig. 1), which is not prominent for nonlexical stimuli. That is, probably because understanding lexical stimuli is more crucial as well as attention-consuming in CI users than in NH controls, attention control mediated by the SN in CI users may have resulted in broader activation of the A1/A2 as compared with NH controls who could process lexical stimuli with less effort. Additionally, as a corollary to effortful interpretation of distorted lexical signal, the left PHG in the CI user group may have been activated to retrieve semantic memory [Kirwan et al., 2009; Whatmough and Chertkow, 2007].

The included studies used different types of lexical stimuli (i.e., sentences or words). Different types of lexical stimuli may have affected the result to some extent, because cortical regions such as the anterior temporal lobe are known to be specifically involved in sentence-level

processing in NH people [Hickok and Poeppel, 2007]. However, as in other ALE meta-analyses that used different types of stimuli [Duerden and Albanese, 2013; van der Laan et al., 2011], different types of lexical stimuli used in this study may add information to previously performed individual studies from a holistic point of view.

CI Users Process Nonspeech Sound with Extra Effort: Activation of SN for Nonlexical Stimuli

Meanwhile, for nonlexical stimuli, CI users activated subareas of the SN such as the right insula and left dACC. As in the lexical stimuli condition, CI users in this study may have activated the SN to detect and process nonlexical stimuli with poorly represented spectral and temporal cues. Together with the unique activation of the SN for lexical stimuli, the CI user group demonstrated much effortful processing of both lexical and nonlexical stimuli as compared with the NH control group.

Of note, CI users showed activations significant in areas at the left A2 but the NH control group at the right A2 for nonlexical stimuli (Fig. 2). This may show that CI users have troubles differentiating lexical and nonlexical stimuli during low level processing due to degraded sound input. The unique activation of the left IFG for the contrast “lexical stimuli–nonlexical stimuli” in the CI user group segregation may also prove that the differentiation between lexical and nonlexical sound is appearing at higher processing levels in CI users. In this regard, the insula and dACC may have been activated to better detect sound stimuli, although the stimuli presented were nonlexical.

Strength and Limitations of this Study

To the best of our knowledge, this is the first study that used a coordinate-based ALE meta-analytic approach to systematically determine consistency across PET studies on speech and nonspeech sound perception in CI subjects. By minimizing study-to-study disparities with regard to paradigm, we attempted to see common neural correlates for sound processing in CI users. The principal strength of this quantitative meta-analysis is that it is based on multiple peer-reviewed studies, in our case with 58 CI patients with 92 peak coordinates as well as 45 NH subjects with 40 coordinates. Thus, the results from the present CI-related brain activation maps are more robust than those of any individual imaging study on sound perception in CI users. Also, by comparing the results of CI users with those of NH controls, we have reconfirmed similarities and disclosed disparities in the two groups with regard to speech and nonspeech sound processing strategy.

However, limitations of this study should be addressed. First, a limitation of the ALE analysis is that it does not take into account the level of statistical significance and the cluster size. However, it is unlikely that the variation

in statistical thresholds has otherwise significantly biased the obtained results because false positives from a single study are averaged out when multiple studies are combined. Second, because only two studies [Coez et al., 2008; Mortensen et al., 2006] included poor performers, we could only investigate neural correlates of good performers. Also, we could not adopt a contrast “nonlexical stimuli–lexical stimuli” because only one study [Mortensen et al., 2006] provided results from the contrast. Future meta-analysis of poor performers and comparison to the results of this study may enable us to further understand sound processing mechanisms and critical factors for good performance in CI users, and future meta-analysis using the contrast “nonlexical stimuli–lexical stimuli” may further prove the role of alertness in CI-assisted sound processing. Third, the effect of the side of CI could not be explored because all but one study [Wong et al., 1999] included both right- and left-CI users. Although previous researchers reported that neither the side of CI nor the number of active electrodes had a significant effect on the brain regions activated in previous studies [Giraud et al., 2001; Naito et al., 2000], future meta-analysis comparing the effect of the side of CI on cortical activity may give us additional information. Furthermore, subtraction analyses such as “CI (lexical–baseline)–NH (lexical–baseline)” or “CI (nonlexical–baseline)–NH (nonlexical–baseline)” did not show significant foci of relative activation because the number of included studies was not enough for yielding significant results [Eickhoff et al., 2011]. To further explore the differences between the two groups using subtraction analyses, future follow-up meta-analyses on larger number of studies should be performed. Finally, a longitudinal study with serial functional imaging study may further elucidate the change in the level of attention needed to process sound provided by CI.

CONCLUSION

Taken together, previous episodic observations on lexical stimuli processing using the dual auditory stream in CI users were reconfirmed in a meta-analytic level by this study. However, this study also suggests that dual-stream auditory processing in CI users may need support from the SN. In other words, CI users need to pay extra attention to cope with degraded auditory signal provided by the implant, although they use the same dual-stream pathways as NH peers do.

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