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The response of the central auditory system to nonsense syllables in normal hearing adults with and without HIV/AIDS: an fMRI study

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Abstract

Aim The aim of this study was to apply fMRI to comparatively evaluate any activation in the central auditory nervous system (CANS) to nonsense syllables sound in normal hearing adults with and without HIV/AIDS.

Objective To determine the response of the central auditory nervous system (CANS) to nonsense syllables sound in normal hearing adults with and without HIV/AIDS, using fMRI.

Method A between-group comparative design was used to determine and compare the response of the CANS to nonsense syllables stimuli of a sample of 15 normal hearing participants without HIV/AIDS and 12 normal hearing participants with HIV/AIDS. Structural and fMRI images were acquired during a listening task where nonsense syllables were presented binaurally using earphones. Stimuli were presented with a block design with two conditions: silence (baseline) of twenty seconds, and the stimuli task tone of twenty seconds. Each block was repeated four times. The blood oxygen level-dependent (BOLD) technique was employed.

Results Both groups showed activation in all the region of interests (ROIs) of the CANS. The mean percentage signal change in BA41 and BA42 differed significantly between the two groups with a p-value of 0.03. The control group showed a significantly greater increase in neuronal activity caused by cerebral blood flow than the HIV/AIDS group.

Conclusions This study indicates that BOLD fMRI provides the possibility to display brain regions responding to specific auditory stimuli applied during the scanning session. These differences could not have been observed with any other basic audiometric test procedure.

Keywords blood oxygenation level dependent (BOLD), cluster of differentiation 4 (CD4), binaural, Brodmann areas, Wernicke's area

INTRODUCTION

Modern brain imaging techniques have had a great impact on the study of the human central auditory function. Magnetic resonance imaging (MRI) has become one of the most significant non-invasive methods for investigating human brain structure and functional changes. It has a much-improved spatial sensitivity and specificity, and it can map auditory responses with sufficient topographic detail. The results can justify the investigation of longer-term dynamic processes, such as functional changes after disease, damage, retraining, or therapy.[1] Although functional imaging of the central auditory pathway has not been widely used in ear, nose and throat (ENT) or audiology departments, a growing literature on its potential application is being developed. During the past 20 years, neuroscience of the auditory system has progressed so far that we are now able to understand the functional structure of the auditory system in normal hearing persons as well as in those with hearing loss. Imaging methods are suitable for use with both children and adults. In the case of functional magnetic resonance imaging (fMRI), several observations can be conducted with the same person; accuracy is improved by mapping the activation of the brain structure specific to that patient.[2] fMRI measures the brain function and neural activity for longer than a specific time range in a picture format.[3] Brain function and brain changes have become significant areas of research in the field of audiology. Auditory fMRI can be used to investigate functional changes in the auditory system,[4] and gain insight into the functional changes that can occur in the central auditory nervous system (CANS).[5]

The aim of the study was to employ fMRI to determine the response of the CANS region of interest (ROI) to nonsense syllables in normal hearing adults with and without human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS), and then to determine whether the cluster of differentiation 4 (CD4) count and antiretroviral therapy (ART) had any effect on the neural response of CANS (ROI) to auditory stimulation in the HIV/AIDS group.

MATERIAL AND METHODS

The study was conducted over five years (2011 to 2016). Hearing test results were obtained to determine the hearing ability of each potential participant. In order to confirm normal hearing, conventional (250Hz-8000Hz) pure tone audiometry was performed. Those who could hear pure tones of 25 dB or lower across all frequencies were considered to have normal hearing. HIV/AIDS and control participants, all with normal hearing, were selected to take part in the study

Twenty-seven (n=27) participants were included in the study: 12 HIV positive (mean ± standard deviation) (M ± SD = 32.8 ± 6.5yrs), and 15 HIV negative control participants (M ± SD = 25.67 ± 5.6). All participants who met the selection criteria were required to attend the ENT department at a hospital in Pretoria, South Africa. The HIV/AIDS group attended the

infectious disease clinic at the hospital in Pretoria South Africa. All the participants were tested for HIV/AIDS to confirm their HIV/AIDS status. They were requested to participate in the study on a voluntary basis. If they agreed they were asked to sign a consent form.

• *MRI protocol*

Structural and functional MRI (fMRI) images were acquired using a 1.5T Siemens Magnetom Espree. Earphones were fitted on each participant's head covering both ears for the auditory stimuli that were presented to both ears. The 3D volume of an fMRI scan of the head was imaged every one or two seconds. This produced hundreds or thousands of completed images per scanning session. These data represent information about the anatomy of the brain, and are used for processing and analysis using algorithms and statistical methods.[6] The MRI acquisition parameters are summarised in Table 1. All scans were acquired using the head coil HE.

• *Functional MRI experimental task*

During the fMRI scan, participants were instructed to lie down with their eyes closed and listen to the binaural auditory stimuli comprising 'nonsense' syllables. Twenty second (20s) blocks of nonsense syllables were alternated with 20s blocks of silence.

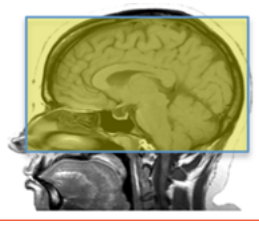
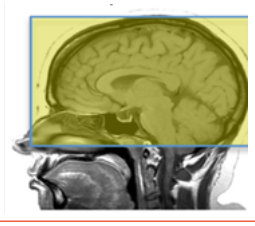
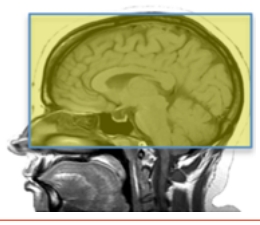
• *Data analysis*

BrainVoyager was used to perform automatic brain segmentation, surface reconstruction, cortex inflation, and flattening. Pre-processing of functional data comprises several steps including mean intensity adjustment, slice scan time correction, 3D motion correction, spatial smoothing, and temporal filtering.[7] The Talairach transformation was needed for both anatomical and functional data for multi-subject analysis.[7] Each participant's functional data sets were co-registered to his/her high-resolution anatomical MRI. The statistical analysis test was performed to determine which voxels in the brain were significantly activated by the nonsense syllables task. BrainVoyager software provides a multi-subject statistical analysis. This software uses general linear model (GLM) for single subject analysis specifying statistical models. The analysis is obtained by adding several explanatory variables known as predictors, which give precise activations. GLM analysis is a univariate method performed independently on each voxel. Time course and beta values are estimated for each voxel.[8] The end result of the statistical analysis is a statistical map that shows which voxels are significantly activated given a specified statistical threshold. The 'threshold' statistical map can be overlaid directly onto the functional (FMR) data, co-registered anatomical volumetric MR (VMR) data, or surface module for visualisation.[7]

• *Statistical analysis*

A statistical analysis method currently used in fMRI research combines the traditional p-value threshold with a required minimum number of contiguous voxels (commonly referred to as a 'cluster size threshold').[9] Statistical methods are a helpful tool to interpret the information from neural imaging data into statistical data.[6] A spreadsheet was created in Microsoft Excel® to combine all the participants' data, the ROIs, and the whole brain activation areas, so that they could be imported into a spreadsheet in the statistical analysis programme SPSS (IBM SPSS Statistics for Macintosh Version 23.0).[10] The independent sample test (t-test), a test of significance, evaluates the differences between the means obtained from the two groups. The two groups (control and HIV/AIDS) were evaluated with the difference of means of the ROIs' areas in the nonsense tasks. Separate analyses for participants were performed on the average signal in each ROI using the GLM.[10] A one-tailed test is a statistical test in which the critical area of a distribution is one-sided so that it is either greater than or less than a certain value, but not both. If the sample being tested falls into the one-sided critical area, the alternative hypothesis will be accepted instead of the

Table 1. MRI acquisition parameters

	t1_mpr_tra_iso Pulse sequence type	**gre_field_mapping Pulse sequence type**	**ep2d_bold_moco_NS Pulse sequence type**
	Tfl	gradient	ep2d_bold
	Area of acquisition	Area of acquisition	Area of acquisition
Area of aquisition			
Field of view (mm)	250	250	250
Matrix	256 x 256	64 x 64	64 x 64
Slices	1 slab (176 slices)	28	28
Slice thickness (mm)	1	4	4
Acquisition orientation	Axial	Axial	Axial
Phase encoding direction	R-L	A-P	A-P
Order of Acquisition of slices	sequential, ascending	interleaved	interleaved
TE	3.02ms	(1) 4.76 (2) 9.52	30ms
TR	1650ms	513ms	2000ms
Flip angle	15°	60°	80°

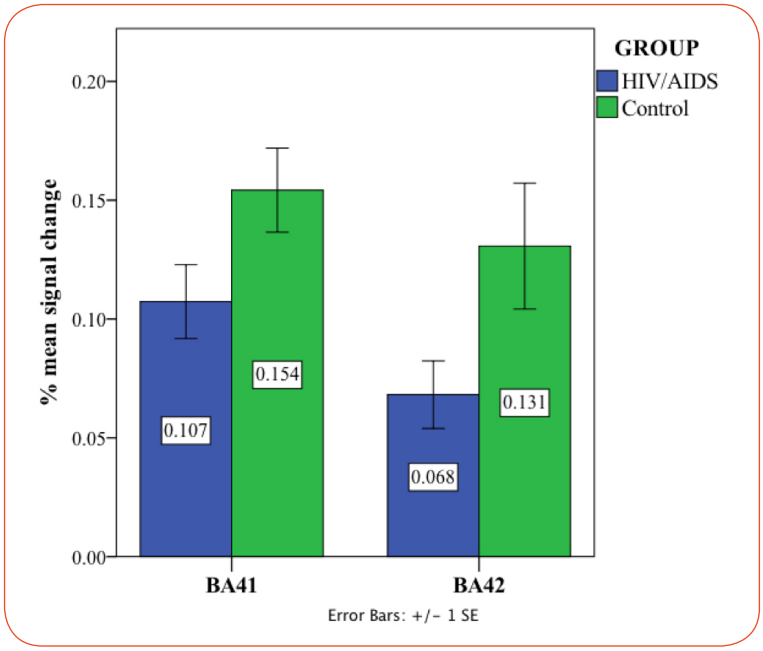


Figure 1. Mean percentage signal change during the nonsense syllables task in BA41 and BA42.

null hypothesis. An unpaired t-test was used to examine the significance of differences between the means of continuous variables between two groups of the ROIs.

The p-values were also determined. If the p-value was smaller than a predetermined alpha level (0.05) it was considered to be statistically significant.[11] The UNIANOVA procedure provides a regression analysis and analysis of variance for one dependent variable by one or more variables.[10] UNIANOVA was conducted to determine if gender, age, and education played a differentiating role in r-square and linear regression (CD4 count and years on ART) and analysis of variance (ANOVA) was also performed to examine associations between brain activation and percentage signal change during presentation of auditory stimuli (ROI areas were used).[10] The t-test used both groups (control and HIV/AIDS) in all the ROIs and Brodmann areas BA41 and BA42 was significant.

RESULTS

In order to explore the data, regarding the response of the CANS to nonsense syllables, it was necessary to perform a ROI analysis of the CANS areas in the brain. The results focused on the defined anatomical ROIs areas (cochlear nuclei (CN), SOC, IC, MGN, BA41 and BA42) for which mean values for all voxels in the particular ROI area were calculated at a given point in time. A priori ROIs for the auditory pathway were defined, based on the study[13] of structural brain changes in tinnitus. ROIs were defined as spheres with radii of 5.0 mm (8.0 mm for the medial geniculate nucleus), centred on the MNI co-ordinates for the ventral and dorsal cochlear nuclei (±10, -38, -45), superior olivary complex (±13, -35, -41), inferior colliculus (±6, -33, -11), medial geniculate nucleus (±17, -24, -2), and the primary and secondary auditory cortices corresponding to Brodmann areas 41, 42, and 22. The cortical areas were defined based on the Talairach brain atlas[12] in BrainVoyager. The Montreal-Neurological Institute (MNI) coordinates were transformed into Talairach coordinates using BrainMap (http://www.brainmap.org/ale/). As illustrated in Figure 1, it was evident that the control group showed more activation than the HIV/AIDS group in both areas. In these two groups' activation areas BA41 (anterior transverse temporal area) and BA42 (posterior transverse temporal area) were presented in both hemispheres of the brain. There was a statistically significant mean difference in the activation of BA41 t (25) = -1.96, p = 0.03 in the HIV/AIDS group (M = 0.107, SD = 0.054) and the

Table 2. Difference between the groups for BA41 and BA42 as determined by the one-tailed t-test

Area	Group	n	Mean	Std Deviation	Std Error Mean	95% CI for Mean Difference		t	df	*p*
						Lower	Upper			
BA 41	HIV/AIDS	12	0.107	0.537	0.015	-0.967	0.002	-1.9	25	0.03*
	Control	15	0.154	0.068	0.017					
	Total	27	0.133	0.066	0.013					
BA 42	HIV/AIDS	12	0.068	0.049	0.014	-0.129	0.004	-1.9	25	0.03*
	Control	15	0.131	0.103	0.026					
	Total	27	0.103	0.088	0.017					

**Note. p ≤ 0.05 significant difference*

Table 3. Influence of gender, age and education on the level of activation in BA41

Area BA 41	df	Mean Square	F	p
Effect of **gender** (male = 9, female = 18)	1.00	0.02	4.65	0.04*
Effect of **age** (21-30 = 18, 31-40 = 6, 41-50 = 3)	1.00	0.00	0.00	0.95
Effect of **education** (matric = 11, post matric = 16)	1.00	0.00	0.18	0.68

** Note. Significant difference at the p ≤ 0.05 level*

Table 4. Influence of gender, age and education on the level of activation in BA42

Area BA 42	df	Mean Square	F	p
Effect of **gender** (male = 9, female = 18)	1.00	0.03	4.92	0.04*
Effect of **age** (21-30 = 18, 31-40 = 6, 41-50 = 3)	1.00	0.00	0.04	0.85
Effect of **education** (matric = 11, post matric = 16)	1.00	0.00	0.00	0.99

** Note. Significant difference at the p ≤ 0.05 level*

control group (M = 0.154, SD = 0.068). There was also a statistically significant mean difference in the activation of BA42 t(25) = -1.13, p = 0.03 between the HIV/AIDS group (M = 0.068, SD = 0.049) and the control group (M = 0.154, SD = 0.068) (see Table 2). The results were compared according to the possible confounding influences such as gender, age, and education on the mean percentage signal change in BA41 and BA42 for the two groups. Since it has been shown that auditory fMRI results may be influenced by gender,[11] age,[14] and educa tion,[15] it was important to establish if these effects were also noted in the current data. Table 2 presents the results of the one-way between-participants ANOVA for the mean percentage signal change in BA41 and BA42 for gender, age, and education. The results in Table 3 indicate that age (BA41 p = 0.95 and BA42 p = 0.85), and education (BA41 p = 0.68 and BA42 p = 0.99), had no statistically significant effect on the mean percentage signal change in BA41 and BA42. However, gender had a significant effect at the 5% level of statistical significance for BA41 and BA42 with a p-value of 0.04. The data were computed to determine whether the CD4 count and ART had any effect on the neural response of CANS (ROIs) to auditory stimulation in the HIV/AIDS group.

The focus was the areas in which significant differences were obtained (ROI), namely BA41 and BA42. The variance of the data is explained by the fitted regression line. The effects of CD4 count on the activation of BA41 and BA42 were investigated. It was considered relevant to determine whether the CD4 count had any effect on the neural response of the CANS (ROIs), namely BA41 and BA42 to auditory stimulation in the HIV/AIDS group. As noted, the results of the current study disclosed that HIV/AIDS disease severity, in terms of the CD4 count and the activated BOLD signals in BA41 and BA42 area during the nonsense syllables task, showed a trend: the higher the CD4 count in the HIV/AIDS group, the lower the activation of the signal change in BA41 or BA42 (see Figure 2). An inverse correlation was found between the years on ART and the activated blood oxygen level-dependent (BOLD) signals in BA41 and BA42 areas during the nonsense syllables task. The random effects linear regression model in SPSS showed inverse correlations between the mean percentage signal change in BA41 or BA42 and ART use in years. As the use of ART in years increases, the mean percentage signal change in BA41 or BA42 decreases (see Figure 3). This negative response to the mean percentage signal change reflects a decrease in oxygen consumption and neural activity, which can be induced by a reallocation of blood flow from the less demanding areas to the most demanding regions in the brain.

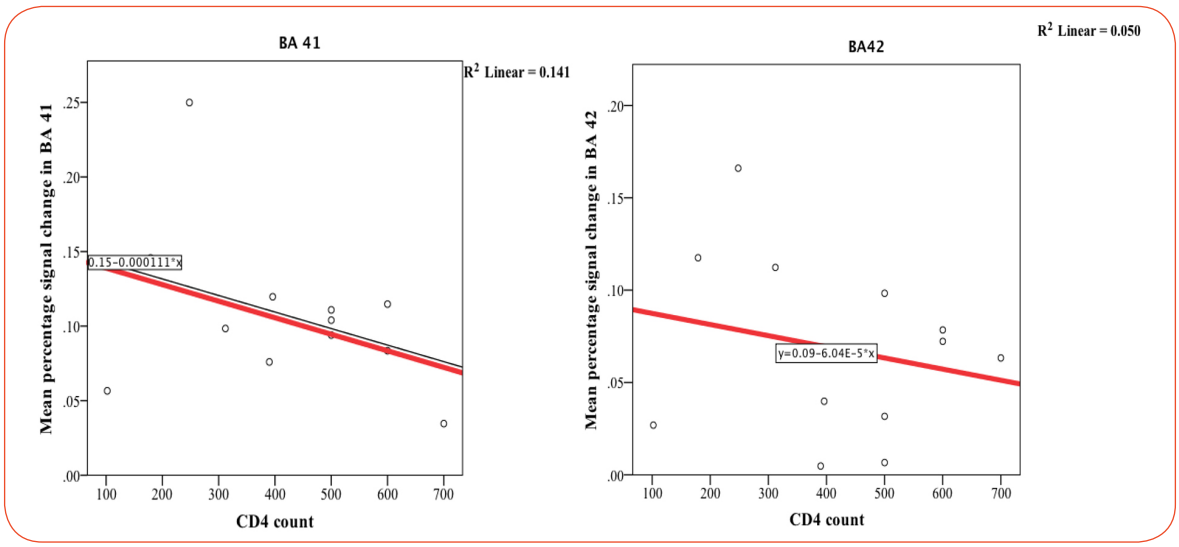


Figure 2. The linear regression between CD4 count and the mean percentage signal change in BA41 and BA42.

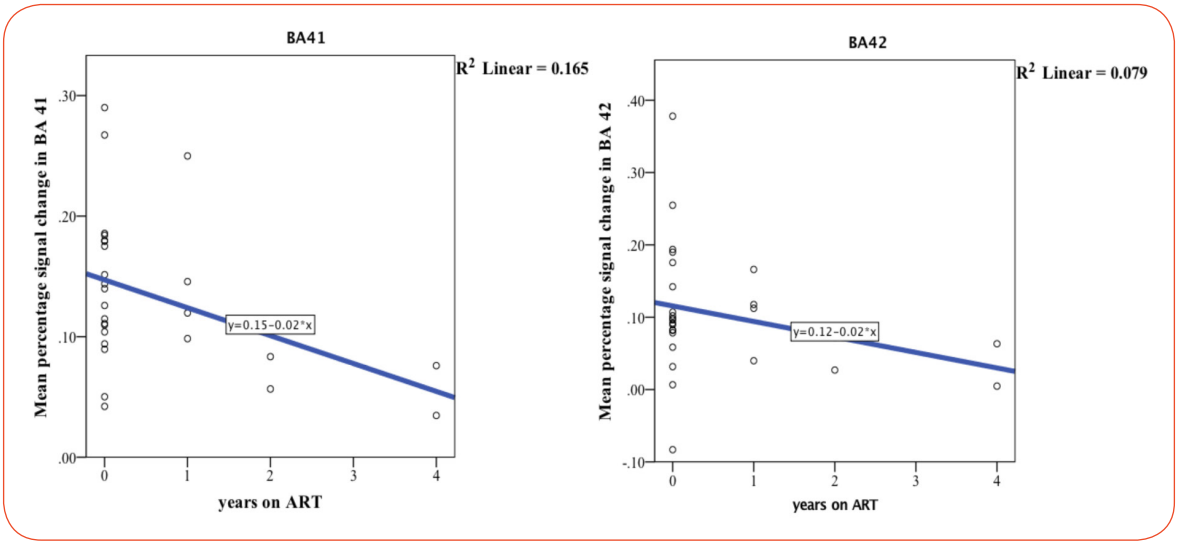


Figure 3. Relation between years on ART and mean percentage signal change in BA41 and BA42.

DISCUSSION

In terms of the results it is suggested that the degree of under connectivity in people with HIV/AIDS depends on the task requirements and the brain regions recruited for the task. The primary auditory cortex (PAC) includes the areas of BA41 and BA42. The PAC showed sensitivity to speech sounds, which is not surprising since it is involved in phonological processing.[16] The findings of this study showed that BA41 and BA42 activation was more significant with nonsense syllables. Bernal and Altman[16] consider BA41 and BA42 to be part of the perceptual language area, and they point out that language can be left-lateralised, as in the participants of their study.[16] Binaural interaction with sine tones for auditory processing is a simple method for activating Heschl's gyrus and the planum temporale.[11] The function referred to as phonological processing (phoneme recognition) is found in the BA41 and to a lesser extent in the BA42 region. Heschl's gyrus is the intersection area where auditory processing (auditory stimulus) and language processing (meaning) occur.[17] Both BA41 and BA42 have perceptual functions and are part of the main language processing area also known as Wernicke's area. Wernicke's area includes BA21, BA22, BA41, and BA42. These areas are partly responsible for language processing and recognition.[2] HIV/AIDS participants showed thinner cortical thickness, smaller cortical volumes, and larger ventricular size than control participants. This could be related to the degree of neurocognitive impairment.[18] fMRI studies can be valuable to observe or detect functional changes in specific areas, such as BA41 and BA42 in this study.

Neuroimaging techniques such as fMRI produce maps of cortical activation relying on changes in hemodynamic variables occurring in close proximity to localized increases of neural activity.[19] Fluctuations in the BOLD response within specific brain regions reveal a decrease or increase in neuronal activity as determined by cerebral blood flow to those specific areas under investigation. A decrease in activation, which is caused by less oxygenated blood flow to the regions, might thus be an indication of less activity in this area.[18] In a Polish study[19] the results indicated smaller or less activation within specific brain areas in participants with central auditory processing disorder (CAPD), where the display was smaller or less activation was observed within certain areas of the brain. In a review study of functional MRI in HIV[14] it was reported that participants with HIV/AIDS showed hyper activation in task-related brain regions compared to the control group.

The results of another study[19] indicated smaller or less activation within specific areas in the brain areas of participants with CAPD compared to controls. The display was smaller or less activation was observed within certain areas of the brain. The difference in brain activity noticed in participants in this study might be on account of the different behavioural patterns to be observed in participants with CAPD and HIV/AIDS.

Kallail and colleagues[20] reported that people with HIV/AIDS manifested cognitive impairments related to the central nervous system as well as communication deficits even if they were fairly healthy. A high prevalence of cognitive and language deficits and central auditory disturbances was found in persons with HIV/AIDS. The cognitive impairments had an effect on speech, language, and hearing, which influenced their communication abilities. Additional research on how the communication ability of people with HIV/AIDS is affected is necessary to maintain and improve their communication skills and quality of life.[20]

HIV associated neurocognitive disorder (HAND) is a collective term for neurocognitive disorders caused by HIV/AIDS.[21] HAND starts sub-clinically before it progresses to a symptomatic stage (the primary disease or disorder).[14] BOLD fMRI has proved to be a sensitive tool to detect abnormal brain function in an early stage and might therefore be a useful tool to evaluate the effect of HAND on brain function).[14] It has been shown that HAND can cause low concentration, memory loss, mental slowness, and decrease in motor symptoms.[21] A comprehensive neurocognitive evaluation for HAND should therefore involve the five neurocognitive areas: verbal/language, attention/working memory, abstraction/executive function, learning/recall, rate of information processing, and motor skills. The significant difference in activation in the ROIs found in this study, in response to the presentation of nonsense syllables, should be investigated further to deter-

mine if activation changes can be seen as underlying the differences in functioning found in the research discussed above.

In general, then, there seems to be consensus in the literature concerning the response of the CANS to nonsense syllables, bearing out the results obtained in this study. Determining the response of the CANS to sound in persons with HIV/AIDS could ultimately contribute to ensure better diagnosis and better service delivery. Damage to BA41 and BA42 causes auditory verbal agnosia (pure word deafness). People with auditory verbal agnosia can hear a speaker talking, but cannot understand what is being said. Auditory verbal agnosia can present as the result of acute damage or as a result of chronic progressive degeneration over time. Auditory verbal agnosia can also present as a symptom of neurodegenerative disease. The current predicament is that HIV/AIDS does affect the CANS. These changes have not been explored sufficiently and should therefore be investigated and documented. While cortical deafness is a rare disorder that is not easily detectable on MRI, dysarthria pathology does occur in BA41 and BA42. The observed functional alterations contribute to the severe cognitive changes that are associated with HIV/AIDS.

It was confirmed in a recent study[22] that individuals with HIV/AIDS may have central auditory processing deficits that correlate with the cognitive deficits observed in these individuals. Since HIV/AIDS infection may damage central auditory pathways, central auditory tests could be useful to diagnose or track central nervous system effects of HIV/AIDS. The study showed that HIV/AIDS affects several areas of the brain that are involved in central auditory processing, particularly the thalamus, internal capsule, and temporal cortex. The thalamus contains the medial geniculate body, and this finding may be relevant for auditory processing.[22]

The response of the CANS to sound in persons with HIV/AIDS ultimately contributes to an enhanced diagnosis and improved service delivery. The role of fMRI in a clinical context is as yet limited, although it is becoming increasingly important for mapping brain functions in individuals (especially for demarcating speech related regions) prior to surgical treatment of brain tumours. As more detailed knowledge is obtained about the various functions of the brain, more clinical applications of fMRI may emerge.[12]

From the foregoing discussions it is clear that the current predicament is that HIV/AIDS can affect the CANS. These changes have however not been explored and should therefore be investigated and documented. The findings of a 2008 study[23] were that HIV/AIDS participants using ART demonstrated an inverse correlation between CD4 count and functional BOLD signal. The use of ART had no effect on the BOLD signal in fMRI examination.

CONCLUSION

Based on the MR findings in this study, it is reasonable to assume that individuals with HIV/AIDS may have central auditory processing deficits. Since HIV/AIDS infection could damage central auditory pathways, central auditory tests may be useful to diagnose or track central nervous system effects of HIV/AIDS. Also, it is reasonable to assume that central auditory processing deficits will correlate with the cognitive deficits in patients with HIV/AIDS, which means that central auditory tests may provide a new way to assess central nervous system function in individuals with HIV/AIDS.

The idea that HIV/AIDS can affect the CANS is supported by the findings of this study; they reinforce the potential of auditory fMRI to assess the CANS in people living with HIV/AIDS. It is safe to assume that auditory fMRI will play an important role in the development of new techniques for clinical application in the near future.

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