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Dichotic listening in patients with situs inversus: brain asymmetry and situs asymmetry

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Abstract

In order to investigate the relation between situs asymmetry and functional asymmetry of the human brain, a consonant-vowel syllable dichotic listening test known as the Standard Dichotic Listening Test (SDLT) was administered to nine subjects with situs inversus (SI) that ranged in age from 6 to 46 years old (mean of 21.8 years old, S.D. = 15.6); the four males and five females all exhibited strong right-handedness. The SDLT was also used to study twenty four age-matched normal subjects that were from 6 to 48 years old (mean 21.7 years old, S.D. = 15.3); the twelve males and twelve females were all strongly right-handed and served as a control group. Eight out of the nine subjects (88.9%) with SI more often reproduced the sounds from the right ear than sounds from the left ear; this is called right ear advantage (REA). The ratio of REA in the control group was almost the same, i.e., nineteen out of the twenty-four subjects (79.1%) showed REA. Results of the present study suggest that the left-right reversal in situs inversus does not involve functional asymmetry of the brain. As such, the system that produces functional asymmetry in the human brain must independently recognize laterality from situs asymmetry. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Laterality; Handedness; Speech dominance; Iv; Inv

1. Introduction

The human brain is asymmetric functionally as well as anatomically, but still unknown is what kind of mechanism creates this functional and/or anatomical asymmetry of the brain. Most people are right handed and language dominance resides in the left hemisphere [21]. Many hypotheses that explain the origin of the asymmetry have been presented [7, 9, 17], and there are still others that assume a relationship between left brain dominance and situs asymmetry [12, 22].

Situs inversus is a rare anomaly observed in about one in 10,000 human beings; mirror-reversal occurs in the respiratory, digestive and vascular organs [29], but no functional impairment is caused by this condition. Therefore such an anomaly can be an interesting paradigm for studying the relation between brain asymmetry and situs asymmetry. Included among those diagnosed with SI are patients with Kartagener's syndrome, which is an autosomal trait where the reversal of body asymmetry is associated with bronchiectasis, sinusitis, anosmia, and male sterility [15]. A defect in dynein arms of cilia that leads to impaired ciliary function in patients with Kartagener's syndrome has been demonstrated [1], but ciliary dysfunction does not seem to be directly related to situs inversus. Waite et al. studied Maoris in Samoa and showed that their high incidence of bronchiectasis is caused by ciliary dyskinesia and that situs inversus is not associated with ciliary dysfunction within the population [32]. Among patients with Kartagener's syndrome and their families, situs inversus was diagnosed in about 50% of the patients with ciliary dysfunction, suggesting that laterality was determined by chance [21].

If asymmetric reversal was only limited to internal organs, there would be no point in studying cerebral asymmetry in the patients with SI. However, according to a study on newts, the left habenular nuclei is larger in those that are normal, but the right nucleus is larger in

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newts with SI [33]. This possibly suggests that the reversal of laterality associated with SI in vertebrates involves laterality of the brain, just like that of other internal organs; thus it might be possible that reversal of brain asymmetry does occur in subjects with SI. Handedness, one of the most obvious functional asymmetries of the human brain, does not appear to be involved with situs inversus [29]. Since ratio of left-handedness among subjects with SI is reported to be the same as that in the normal population, the functional asymmetry of the brain in subjects with SI is probably the same as that observed in normal subjects. Although there is a close relation between handedness and speech dominance, it is not overly restrictive: 96% of the right-handed population has left speech dominance, but 70% of the left-handed population also has left speech dominance [24]. Speech dominance seems to be more strictly controlled than handedness, possibly meaning that the functional asymmetry of each is independently controlled. Therefore, even though the handedness among SI subjects is known to be not reversed, it is worth studying functional asymmetry of the brain by using a dichotic listening technique on subjects with SI.

To the best of our knowledge, only two SI cases that relate to our study have been reported, but the results are conflicting. Cohen et al. [6] reported on a 72-year-old right-handed woman who showed aphasia and had a lesion in the right hemisphere (crossed aphasia); they suspect that brain laterality may have been involved in the mechanism of visceral inversion. This case was not situs inversus totalis, but situs inversus ambiguous: the heart and colon were properly located in the patient. Contrarily, Woods [34] found a 62-year-old right-handed man with situs inversus totalis in the records of Washington University Hospital; the patient had a lesion in the left hemisphere and showed aphasia. Woods doubts the possibility that the phenomenon of visceral inversion involves cerebral laterality.

Although very exact in detecting speech dominance, invasive techniques such as a sodium amytal test are unsuitable for this study. Therefore, a DLT was adopted as the method for detecting functional cerebral asymmetry. Right ear advantage (REA) is a common finding with DLTs, i.e., subjects reproduce sounds from the right ear more often than from the left ear. REA is attributed to left hemisphere specialization for language processing [5], and has been explained by Kimura as follows: the auditory input to the contralateral hemisphere is more strongly represented in the brain, and the left hemisphere is dominant for language in most right-handed subjects [16].

Though almost 96% of right-handed people have left speech dominance [24], the reported percentage of REA with a DLT for right-handed subjects has consistently been about 80% [25, 14, 28]. The reason for this discrepancy is thought to be that a DLT detects not only the structural asymmetry of auditory and speech dominance, but also various other cognitive components, such as attention, arousal and spatial orientation [14]. Strauss et al. [27] demonstrated a relation between lateralized language determined by using a carotid amytal test and the result of verbal dichotic listening task. Whereas patients with left hemispheric speech dominance showed a right ear advantage, patients with right hemispheric speech dominance did not show a consistent ear advantage. This data suggests that a DLT may be a reliable measure of lateralized functions and that in addition to language lateralization, other elements such as attention determine ear advantage. Considering these properties of dichotic listening, we used a DLT in order to detect functional asymmetry of the brain.

2. Materials and methods

We found eleven subjects who have been diagnosed as situs inversus totalis with no severe complications and that have been followed by the National Cardiovascular Center (Osaka, Japan) or other hospitals. Two of the subjects were excluded based on the results of preparatory examinations: one had a history of correcting handedness, and the other had a slight hearing defect in one ear. The nine subjects selected were four males and five females ranging in age from 6 to 46 years old (mean of 21.8 years old, S.D. = 16.3). Cases 1 and 2 were 6 years old and Case 3 was 7 years old; all of them found through the national screening of electric cardiograms given to first grade elementary school students. Case 5 was diagnosed as having Kartagener's syndrome with bronchoectasis and chronic sinusitis. All of the subjects were the only SI patient among their immediate family or relatives. The diagnosis of SI was based on at least a chest X-ray showing the reversal of the heart, lungs, bronchus, aortic arch, stomach, and liver, and an abdominal echo examination of the liver, gall bladder, spleen, pancreas, and abdominal vessels.

As a control, twenty four, age-matched, normal right-handed subjects also participated in the DLT; the twelve males and twelve females were from 6 to 48 years old (mean of 21.7 years old, S.D. = 15.3), and all of them exhibited strong right-handedness. There were nine children, eight 6 years old and one 7 years old, among the normal subjects; they were selected as the control for juvenile subjects with SI. The remaining normal subjects were from 16 to 48 years old. Handedness of both the subjects with SI as well as the control subjects was estimated by using the Edinburgh Inventory [23].

The pure tone thresholds of each subject averaged for 1000 and 4000 Hz were within normal limits, i.e., <20 dB HL. Both the subjects with SI and those in the control group (and in the case of minors, the parents) gave their informed consent to participate in the tests. Dichotic Listening Test

2.1. Dichotic Listening Test

The DLT used in this study was identical to that used in previous study [28]. It consisted of pairs of natural speech, consonant-vowel syllables selected from among the following six: ba, da, ga, pa, ta, ka. At every dichotic trial, each ear was simultaneously presented with a different syllable. The dichotic tape was prepared by digitally converting an original, analog dichotic tape at a sampling rate of 48 kHz. The analog tape has been used in several previous studies [25, 26], and they contain a detailed description of its composition. The intensity of the syllables on the bilateral channels of the digitized tape was adjusted for each dichotic pair by using the level meter of a digital audio tape deck (Pioneer D-05). The duration and intensity of all syllables and the synchronization of the dichotic pair on the left and right channels was verified by using a computer workstation (SPARCstation5, Sun Microsystems) with a digital audio interface (DAT Link+, Townshend Computer Tools) Each syllable was exact 300 ms in duration and the inter-pair interval was 6 s.

First, all of the subjects were tested with binaural stimuli in order to certify basic hearing ability for each item of the test. Next, they practised the 10 dichotic trials. Finally, they were tested by using the 120 experimental trials which consisted of four blocks of 30 trials. Subjects were encouraged to give two responses. The test was administered using a digital audio tape player (SONY WMD-DT1) and stereo-headphones (DENON AHD530) adjusted to a level of about 70 dB by using a RION sound meter. The left-right orientation of the head phones was counterbalanced in an ABBA design to control for any possible systematic differences. From the scores for each ear, the index of laterality (LI) was calculated by using the formula $(R-L)/(R+L)$, where R is the number of correct reproductions for right ear stimuli and L is the number of correct reproductions for left ear stimuli. This index compares the score of one ear to that of the other; a positive value indicates a right ear advantage and a negative value a left ear advantage.

3. Results

Table 1 shows the results. The average LI for the twenty four subjects in the control group was 0.09 (S.D. = 0.12), with indices ranging from −0.04 to 0.32. Nineteen of these normal subjects yielded positive index values, indicating that their right ear scores were higher than their left ear scores. As for the remainder, four yielded a negative LI, i.e., left ear advantage, and one had an LI of zero, meaning that she reproduced the same number of sounds with each ear (no ear advantage). This bias ($P < 0.005$) is highly significant. Former DLT studies about normal right-handed subjects showed almost the same ratio of REA, e.g., Sugishita et al. [28], 40/50, 80% (subjects gave double answers for each trial) and Hugdahl [14], 234/303, 77% (subjects gave a single answer for each trial).

The average laterality index for the subjects with SI was 0.11 (S.D. = 0.09), with indices ranging from −0.05 to 0.25. Eight out of the nine subjects yielded positive index values (they showed REA), and only one showed LEA. The binomial probability of this bias occurring by chance is 0.019. There was no significant difference between the two groups for each test item.

The overall scores for the three juvenile SI subjects (cases 1, 2 and 3) were lower than those for the adult SI subjects. This was also the case for the normal control subjects; the averaged right ear score of the fifteen normal adults (84.1/120, S.D. = 8.7) was significantly higher than that of the nine normal juvenile subjects (64.8/120, S.D. = 11.0, $t(\mathrm{df}=22) = -4.784$, $P < 0.0001$), and the left ear score of the fifteen normal adult subjects (74.6/120, S.D. = 14.3) was also higher than that of the normal juvenile subjects (44.8, S.D. = 7.1, $t(\mathrm{df}=22) = -5.809$, $P < 0.0001$). These differences between the children and adults might be related to the tendency of adult subjects reproducing two syllables during most trials, but juvenile subjects reproducing only one syllables during most trials, even though the examiner encouraged them to give two answers. It seemed rather difficult for the children to give two answers when they were uncertain about what they heard. Very few of the syllables reproduced by the children were wrong answers, but many of those reproduced by the adults were incorrect; this might indicate that the adults utilized a kind of strategy where they did not care about what two answers they reproduced, even when they were not very sure about the syllables.

4. Discussion

Results of the DLT for the subjects with SI showed no substantial difference from those for the control group subjects, and this might imply that at least for dichotic listening, functional asymmetry of the brain does not differ in human beings with or without SI.

How is the cerebral asymmetry created? Wada et al. [31] found that even fetal brains have the same anatomical asymmetry in the temporal speech region as that reported by Geschwind and Levitsky for adult brains [9]. Ultrasound echo examinations of thumb-sucking fetuses showed a strong bias for the right thumb [13]. These anatomical and functional asymmetries observed in fetuses suggest that brain asymmetry is controlled genetically. McManus's theory and/or Annet's theory adequately explain the observed pattern of the inheritance of handedness in humans, including the existence of discordance of handedness among monozygotic twins

Table 1
Number and percent of correct identifications during the dichotic listening test, and laterality index (LI) calculated from left and right ear scores. (A) results for each subject with SI. (B) mean and standard deviation (S.D.) of the data gathered from both subjects with SI and control subjects

	Sex	Age	Right ear score	Left ear score	LI[a]	Ear advantage
A						
Case 1	F	6	54/120 (45%)	46/120 (38%)	0.08	REA[b]
Case 2	F	6	56/120 (47%)	39/120 (33%)	0.18	REA
Case 3	M	7	63/120 (53%)	38/120 (32%)	0.25	REA
Case 4	F	15	78/120 (65%)	56/120 (47%)	0.16	REA
Case 5	F	17	98/120 (82%)	85/120 (71%)	0.07	REA
Case 6	M	18	85/120 (71%)	78/120 (65%)	0.04	REA
Case 7	M	36	82/120 (68%)	62/120 (52%)	0.14	REA
Case 8	F	45	66/120 (55%)	73/120 (61%)	−0.05	LEA[c]
Case 9	M	46	78/120 (65%)	68/120 (57%)	0.06	REA
B. Mean (S.D.)						
Subjects with situs inversus						Overall REA ratio
Total		21.8 (16.3)	72.6 (14.4)	59.1 (16.3)	0.11 (0.09)	8/9 (88.9%)
Control group						
Total		21.7 (15.3)	76.9 (13.4)	63.4 (19.0)	0.11 (0.12)	19/24 (79.2%)
Children group[d]		6.1 (0.3)	64.8 (11.0)	44.8 (7.1)	0.18 (0.14)	8/9 (88.9%)
Adult group[e]		31.0 (11.7)	84.1 (8.7)	74.6 (14.3)	0.07 (0.09)	11/15 (73.3%)

[a] LI: laterality index, calculated by using the formula $(R-L)/(R+L)$, where R is the number of correct reproductions of right ear stimuli and L is the number of correct reproductions of left ear stimuli.
[b] REA ([c] LEA): right (left) ear advantage, the sounds from the right (left) ear are reproduced more often than sounds from the left (right) ear.
[d] Children's group consisted of eight 6-year-old and one 7-year-old subjects.
[e] Adult group consisted of 15 subjects from 15 to 48 years old.

[20]. This raises the question, how does the system controlled by those proposed genes know which is right and which is left, even when the situs asymmetry is reversed?

Corbalis proposed the existence of a graded putative substance in the cytoplasm of oocyte as the informational source for laterality [7]. According to his hypothesis, the system for functional brain asymmetry and that for situs asymmetry must independently recognize the bias from each other; otherwise, the sensor for laterality bias of the system for situs asymmetry functions abnormally, whereas that of brain asymmetry works correctly. It is also possible to assume that one substance creates laterality bias for the brain and another does for situs. Although the genes that play a role in producing asymmetries in the human body have not been found yet, some of them must be related to producing or detecting laterality bias.

Two genes related to SI, iv and inv, have been found in mice [4, 30]. The iv gene is reported to cause SI at a 50% rate in the homozygous state; this is interesting as an analogy to the randomness with which SI occurs in humans with ciliary dysfunction, though iv mouse are reported to have no ciliary dysfunction [11]. Furthermore, body laterality is randomly determined in the homozygouts of iv mice [17]. Compared to the iv gene, the inv gene works in a different fashion. Inactivation of inv causes SI at a 100% rate, so Yokoyama et al. [30] proposed the existence of a default pathway to produce normal laterality; inactivation of inv blocks this pathway and causes the reversal of laterality. If Yokoyam et al.'s hypothesis of default pathway is true, it brings about a further question: 'Then how does the default pathway know body laterality?' McManus predicted that the genes related to brain asymmetry, if they exist, might originate from situs genes; since genes controlling asymmetry must be rare, it is unlikely that they would have separately evolved [20]. How iv and/or inv genes works in creating laterality in mice and what are the functions of those genes homologs in humans remains to be studied in the future.

The genes controlling anatomical and/or functional brain asymmetry might be much newer than the genes controlling situs asymmetry. The asymmetry of situs existed rather early in the lineage of vertebrates, like that of flatfish. Which of those two, anatomical asymmetry or functional asymmetry, is newer? Gannon et al. [8] reported on size predominance of the left planum temporale, a temporal speech region homolog in human beings, compared with the right one in chimpanzees. Considering other reported human-like anatomical asymmetries in hominoid primates or in fossil humans [18, 19], anatomical asymmetry of the brain might have appeared earlier than functional brain asymmetries such as handedness or speech dominance. Instead of the existence of systematic anatomical asymmetry in the brain of hominoid primates, no bias in handedness among them has been reported [2], this strongly suggests that functional asymmetries of the brain occurred last and only in human beings. Whether this occurrence of functional asymmetries originated from or had some kind of relation with anatomical asymmetry seems to be another important topic that needs to be intensively studied in the future.

As an exception on handedness, some toads are reported to have a hand preference at the species level [3]; several types have been reported to use their right hand more often than their left forelimbs, when they try to remove a small piece of paper put on their nose. The reason for the handedness of toads is supposed to originate in an inherent physiological action [22]. When a toad eats something poisonous it vomits, and its stomach comes out and hangs from its mouth; the toad then wipes off its stomach to remove the contents. It has been suspected that this biased usage of forelimbs in primary vertebrates is the origin of handedness in human beings [22]. However, our results, as well as the observed pattern of handedness in SI subjects, suggests no direct relation between situs asymmetry and functional brain asymmetry. The handedness existing in human beings and that in toads most likely evolved from different origins.

Still unknown is what mechanism creates functional brain asymmetries in human beings, and to what extent is the processes of creating those asymmetries common or independent? Many relational or possible factors such as sex steroids have been found. However the basic process of creating functional as well as anatomical asymmetry of the human brain remains to be studied. It might be difficult to draw any conclusions about the relation between situs asymmetry and brain asymmetry only from the present study. However, our data may suggest that there seems to be no reversal of functional cerebral asymmetry in subjects with SI, which in turn suggests that functional brain asymmetry might be produced through a mechanism independent from the mechanisms that create situs asymmetry.

Studying anatomical brain asymmetry in SI patients by using high quality MRI appears to be a very fruitful method. Recent functional MRI techniques also seem very promising in determining noninvasively the speech dominance of subjects by using verbal activation tasks. Further research about these points should give us very important data that will elucidate the mechanisms that create brain asymmetry.

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