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Sex difference in brain nerve conduction velocity in normal humans

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Abstract

Nerve conduction velocity (NCV), the speed at which impulses travel along nerves, has been extensively determined in human peripheral nerves because of its clinical utility. In contrast, almost no studies have been made of human brain NCV.

We determined brain NCVs in the visual nerve pathway for 185 male and 200 female university students ages 18–25 years. In each of three independent test conditions, we found that the mean NCV of male students is about 4% faster than in females ($P \leq 0.0001$ for each condition). These male students also have a shorter reaction time in each of seven different RT tests than do females, even though, on the null hypothesis of equal NCVs, we would expect males to have longer RT times because of their greater physical size. Four of these comparisons are significant at or below the 0.001 level.

These males also increase their NCVs with increasing age, in contrast to females. These sex differences in NCV parallel reported sex differences in age changes in white matter in the brain. These age changes may largely explain these NCV differences.

Keywords: Nerve conduction velocity; Brain; Sex difference; Normal humans; Reaction time

1. Introduction

Impulses travel along nerves at a speed called the nerve conduction velocity (NCV). This velocity has been extensively measured in human peripheral nerves because of its utility in clinical medicine (Liveson & Ma, 1992; Oh, 1993). Appreciably decreased NCV can be an important indicator of nerve injury or disease (Liveson & Ma, 1992; Oh, 1993).

In contrast to peripheral studies, there are almost no published data on NCVs in human brains. PubMed (U.S. National Library of Medicine) and PsycINFO (Cambridge Scientific Abstracts) list only one paper (Reed & Jensen, 1992). This study, on 147 normal male college and university students, age 18–25 years, found that the mean NCV in the visual pathway was 2.00 ± 0.01 m/s (S.E.). This value was obtained non-invasively for each student by dividing the maximal head length (glabella to opisthocranion) by the latency of the pattern-shift visually evoked P100 potential (Chiappa, 1990a, Chapter 3). The latency of the P100 is over the nerve path from the retina to the primary visual cortex (PVC). The PVC origin of the P100 potential has been confirmed by positron emission tomography (Fox, Miezin, Allman, Van Essen & Raichle, 1987). The latency [mean about 100 milliseconds (ms)] obtained by this necessarily indirect approach includes about 50 ms for retinal processing and transmission (retina-optic nerve-optic tract) to the thalamus (Baylor, Nunn & Schnapf, 1987; Lowitzsch, 1989). The remaining approximately 50 ms occurs almost entirely in the optic radiation, the band of very small diameter nerve fibers (Martin, 1984) running from the thalamus to the PVC (Mason & Kandel, 1991). The true NCV in these fibers must be more than the above value because the optic radiation is strongly curved (Bürgel, Schormann, Schleicher & Zilles, 1999; Mason & Kandel, 1991). It is in the range directly observed for the optic radiation in the cat: 1–10 m/s (Martin, 1984); other than (Reed & Jensen, 1992) above, human data for this NCV appear to be lacking. This lack of human brain NCV data suggests that it should be of interest to have further data from the brains of normal humans.

2. Methods

A study using the basic methodology of the above study (Reed & Jensen, 1992) was done on 185 males and 200

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females, ages 18–25 years, who were students in a university in Ontario, Canada. They were unselected, paid volunteers who gave their informed consent. The age distributions for males and females were very similar (mean, median, and mode were 20.4, 20, and 19 years for males and 20.3, 20, and 19 years for females). Subjects were measured for height, weight, head length, visual acuity, and tympanum temperatures. Head length was assessed using a caliper to determine the sagittal distance between inion and nasion (Wickett, Vernon & Lee, 2000), slightly less than maximal distance. Each subject was tested for visually evoked potentials (VEPs) of medium-latency (<120 ms, usually between 90 and 110 ms), the P100, evoked by pattern-reversals (black to white, white to black, of a checkerboard) stimulation. These patterns were presented on the monitor of a Nicolet Spirit instrument (Nicolet Biomedical Instruments, Madison, WI, USA) at a frequency of 2.1 Hz. The recommended conditions of Chiappa (1990a, Chapter 3) were generally followed, except that subjects were tested binocularly, as were the subjects of Reed and Jensen (1992). In contrast to these authors (Reed & Jensen, 1992), who used a single pattern of squares 12.5 mm on a side, each square subtending a visual angle of 43′ at 1 m, we used three sizes of squares: (1) 12.5 mm on a side (43′ visual angle at 1 m), in a 16 × 16 pattern; (2) 6.25 mm on a side (21.4′), 32 × 32 pattern; and (3) 3.12 mm on a side (10.7′), 64 × 64 pattern. For each test pattern, 16, 32, and 64 squares, two stimulations were given, two minutes apart. Artifactual potentials, from eye blinks and other sources, were automatically rejected. Each stimulation series of pattern reversals continued until the participant had viewed 100 non-rejected pattern reversals (in a period of approximately one minute). Luminance level was constant throughout the stimulation. All subjects were tested in the same quiet, darkened room while fixating on a spot in the center of the monitor screen one meter distant from their eyes. Gold cup electrodes were applied, using electrode paste, to the Oz and Fz sites on the subject's scalp (10–20 system); Oz is over the primary visual cortex. A Butterworth filter was used but a 60 Hz notch filter was not. The signal-averaged outputs were scored blindly as to sex and test results by the first author. The latencies of well-defined P100 peaks (from the beginning of a reversal to the corresponding peak potential at the Oz electrode), were recorded to the nearest 0.5 ms. The P100 latencies analyzed for a subject were means (for the two trials) for each of the three test conditions: 16, 32, and 64 squares. These selected subjects were also tested for seven different reaction time (RT) tests using the Cognometer.[2] These tests require subjects to respond quickly to a visual display by pressing a particular key.

[2] Cognometer version 4.00SN, http://www.@brain.com Inc., Newport Beach, CA, USA. It is a reaction time testing program consisting of seven different cognitive tasks: physical reflexes (=simple RT), perceptual reflexes, cognitive reflexes, working memory speed, perceptual acuity, working memory capacity, and visual-spatial reflexes (Odd-man-out). Detailed descriptions of these tests are available from the authors.

3. Results

Regressing P100 latency values within sexes for each test condition on height, weight, age, tympanic temperature, and visual acuity yielded non-significant regressions except for height in the 16 square condition in males ($P = 0.014$) and in the 64 square condition in females ($P = 0.022$). Both correlations with height, *if real* and not Type I errors (they are out of 30 significance tests), very likely result from the general within-subject correlation of measures of size (head length must be closely correlated with the length of the visual pathway which in turn is correlated with P100 latency). The correlation of height with head length in males is 0.29 ($P < 0.0001$); in females 0.23 ($P = 0.001$). At any rate, we do not correct P100 latency values for height because this would affect head length and we use head length, although correlated, to obtain the NCV. It should be noted here that, although skull thickness is a component of head length, males and females do not differ significantly in mean frontal and occipital skull thickness (Lynnerup, 2001; Ross, Jantz & McCormick, 1998).

In Table 1, the mean values of P100 latencies, by test condition and sex, and of head lengths by sex, are presented. For each sex, the mean values increase with increasing number of squares (decreasing square size), in agreement with the literature (Chiappa, 1990c). For each test condition the mean male P100 latency exceeds the mean female P100 latency by one or two percent and mean male head length exceeds mean female head length by 5.9%. In Fig. 1, the mean NCVs for males and females in each test condition are shown. For each condition the mean male NCV exceeds the mean female NCV by slightly more than four percent ($P < 0.0001$).

Note that, because each individual NCV is calculated as (head length)/(P100 latency), if male and female NCVs were on average the same, and if males and females

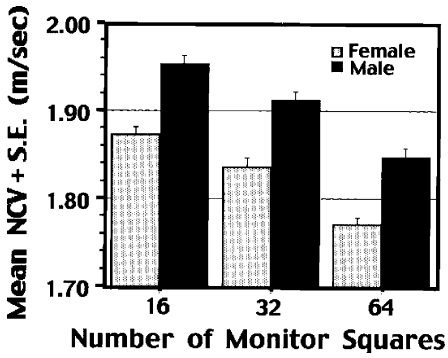

Fig. 1. Mean nerve conduction velocities (NCVs) (±S.E.) for males and females in each test condition. Individual NCVs are calculated as (head length)/(P100 latency) and are in meters/second. The numbers of usable subjects varies from 146 to 170. For each condition, 16, 32, 64 squares, the male and female NCVs are 1.954 and 1.872, 1.912 and 1.836, 1.847 and 1.770, respectively. The S.E.s range from 0.009 to 0.010. The ratios of male mean to female mean are between 1.041 and 1.044, significantly different from one at below the 0.0001 level.

Table 1
Numbers, means, and standard deviations of the P100 latencies, by test condition and sex, and head length by sex

Test condition[a]	Sex	No.[b]	Mean (ms)	Standard deviation	Ratio[c] (male/female)	P[d]
16 squares	Male	154	99.27	3.66	1.012	0.008
	Female	163	98.06	4.36		
32 squares	Male	147	102.00	4.88	1.022	0.0006
	Female	155	99.83	5.95		
64 squares	Male	154	105.10	5.26	1.012	0.028
	Female	171	103.81	5.24		
Head length	Male	185	193.82 mm	9.05	1.059	<0.0001
	Female	200	182.99 mm	9.42		

[a] Test condition: the number of squares in monitor pattern viewed by the subject.
[b] Numbers of usable subjects (those with well-defined P100s from both stimulations in that test condition).
[c] Ratio of male mean to female mean.
[d] P value for difference between male mean and female mean.

Table 2
Correlations of nerve conduction velocities with age by test condition and sex[a]

Test condition	Sex	Correlation	P[b]	P for sex difference[c] in correlation
16 squares	Male	0.208	0.001	0.114
	Female	0.032	0.687	
32 squares	Male	0.217	0.009	0.332
	Female	0.107	0.188	
64 squares	Male	0.225	0.005	0.064
	Female	0.021	0.788	

[a] Numbers are the same as in Fig. 1.
[b] Two-tailed probability of being different from zero.
[c] Two-tailed probability of difference between sexes. The combined *two*-tailed probability for obtaining these three independent P values (Fisher, 1954) is 0.062.

have on average the same ratios of visual pathway length (retina–PVC) to head length (VP/HL), the longer head length of males would be exactly compensated for by their proportionately greater P100 latency. The extensive literature on human brain sexual dimorphism[3] gives no information on possible sex differences in VP/HL. Such differences may exist but there seems to be no a priori reason for this. Because our estimates of brain NCV do differ, we conclude that we have shown that there is a difference in brain NCV between sexes in normal young adults, in favor of males.

Correlations of brain NCV with age, for the three test conditions by sex, are shown in Table 2. The three male correlations are each positive (ranging from +0.208 to +0.225) and are significant; the three female correlations range from +0.021 to +0.107 and are not significant. For each condition the male and female correlations do not differ significantly; the combined two-tailed probability for these three independent comparisons is 0.062 (Fisher, 1954). Fig. 2 shows the mean male and female NCVs for each individual age in each condition; the sex difference is apparent at each age and, more relevantly here, the more or less steady increase in NCV with age in males contrasts with the *decrease* in NCV with higher ages in females. Quadratic regression for women shows significant regression for the 32 squares

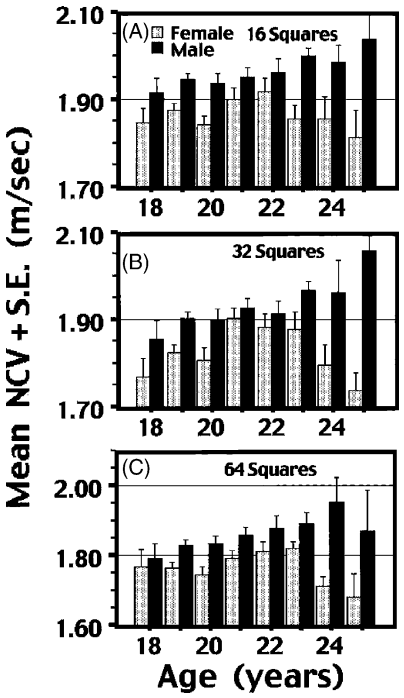

Fig. 2. Distribution of mean nerve conduction velocities (NCVs) (±S.E.) by sex and individual age for each test condition. (A) NCVs for the 16 squares test condition. (B) NCVs for the 32 squares test condition. (C) NCVs for the 64 squares test condition. Note the more-or-less steady increase in NCV with age for males in each condition in contrast to the decrease in NCV in females at higher ages. Quadratic regression for women shows significant regression for the 32 squares condition ($P = 0.0043$, + coefficient for age, − for age^2), but not for 16 or 64 squares, even though Fig. 2 suggests a similar relation there. It is not immediately clear how to interpret this.

[3] On 3 March, 2003 there were 647 abstracts in PubMed (US. National Library of Medicine) for the following Boolean expression [brain AND (sex difference) AND human], for Adults, 19+ years. None gave relevant information on VP/HL.

Table 3
Mean reaction times[a] by sex for seven tests on the Cognometer[b]

Test	Sex	No.	Mean	S.D.	S.E.	Ratio (f/m)[c]	P[d]
Physical reflexes (=simple RT)	Male	171	252.6	30.0	2.3	1.061	<0.0001
	Female	198	268.1	39.3	2.8		
Perceptual reflexes	Male	171	341.2	70.4	5.4	1.086	0.0010
	Female	199	370.4	94.6	6.7		
Cognitive reflexes	Male	171	507.7	91.6	7.0	1.152	<0.0001
	Female	198	585.0	110.7	7.9		
Working memory speed	Male	170	1103.7	220.0	16.9	1.061	0.0104
	Female	198	1171.1	274.2	19.5		
Perceptual acuity	Male	170	400.3	82.9	6.4	1.032	0.1157
	Female	198	413.0	72.5	5.2		
Working memory capacity	Male	168	882.7	256.8	19.8	1.072	0.0223
	Female	197	946.2	269.6	19.2		
Visual-spatial reflexes (Odd-man-out)	Male	171	715.0	259.3	19.8	1.180	<0.0001
	Female	198	843.4	266.9	19.0		

[a] Individual times, in ms, are for the median.
[b] Cognometer version 4.00SN, @brain.com Inc., Newport Beach, CA, USA. Detailed descriptions of the tests are available from the authors.
[c] Ratio of *female* mean to *male* mean.
[d] Probability that the difference in means is significant.

condition ($P = 0.0043$, + coefficient for age, − for age^2), but not for 16 or 64 squares, even though Fig. 2 suggests a similar relation there.

The seven reaction time results are given in Table 3. For each test males had a smaller mean RT than females; four of these differences physical reflexes (=simple RT), perceptual reflexes, cognitive reflexes, and visual-spatial reflexes (=odd-man-out) were significant at the 0.001 level or below.

4. Discussion

The previous published study on brain NCV (Reed & Jensen, 1992) in normal young adult males, using the 16 square test condition and maximal head length, found a mean NCV of 2.00 ± 0.01 m/s. Our value for males in the 16 square condition, using a slightly smaller head length measure (which reduces the calculated NCV) is 1.95 ± 0.01 m/s, in reasonable agreement. Other than (Reed & Jensen, 1992), there appear to be no published data on human brain NCV so there are no published studies reporting sex differences.

Many studies present data on P100 latency of normal subjects but without head length data. One study (Emmerson-Hanover, Shearer, Creel & Dustman, 1994), the largest to date on P100 latency, presents a graph showing mean latency data on 54 males and 44 females 21–35 years of age, using a square (check) size of 30′ (intermediate between our 16 and 32 square conditions), showed a significant sex difference in mean P100 latency: males 105.0 ms, females 102.5 ms (interpreted from their Fig. 3D). An estimate of the approximate mean sex difference in brain NCV in these humans in the studied age range can be derived from these data: the ratio of male latency to female latency is about 1.024; the ratio of mean male head length to mean female head length in our study is 1.059; the ratio of these ratios, 1.059/1.024 = 1.034 should be the approximate ratio of mean male brain NCV to mean female brain NCV in this study, i.e. males about 3.4% faster. This compares with about 4% faster in our study based on individual NCV determinations. Other P100 studies, e.g. (Celesia, Kaufman & Cone, 1987), do not have a large enough sample of males and females in our age range of interest to make similar calculations.

Other types of evoked potential (EP) data are not useful for brain NCV calculation because they lack a measure of the distance over which the observed latency occurs. Auditory EPs (ABR, auditory evoked response) are not reported with this distance and also are from the brain stem, outside the forebrain, and somatosensory EPs are stimulated from the arm or more distally, and this long distance is included in the latency (Chiappa, 1990b, Chapters 5 and 6).

The reaction time results appear to strongly confirm the above brain NCV results, also showing faster brain NCVs for males. On the null hypothesis of equal mean brain (and peripheral) NCVs in males and females, one would expect *greater* mean RTs for males because of their longer nerve pathways due to their greater physical size (the mean height of our male students is 180.68 cm, that of female students is 166.74 cm; the ratio is 1.084). Instead, for each test males had a *smaller* mean RT than females; four of these differences (physical reflexes = RT, perceptual reflexes, cognitive reflexes, and visual-spatial reflexes = odd-man-out) were significant at the 0.001 level or below.

A visual RT can be partitioned into an *input* time (retina to primary visual cortex) of about 100 ms, a brain (cerebral cortices and inter-cortex) time, and an *output* time (motor

cortex to finger tip). This latter time is only about 20 ms because direct measurement of the time from motor cortex to the wrist is about 17 ms (Rossini, Marciani, Caramia, Hassan & Cracco, 1986) and wrist to finger tip is about 3 ms more. Therefore, for each RT test most of the time is spent in the brain *after* reaching the PVC; for the Visual-spatial reflexes, since the male RT mean is 715 ms, this time—the "RT problem solving time"—is about 595 ms or $(715–120)/715 = 0.83 = 83\%$ of the RT in males. For this test in females the RT mean is 843 ms, indicating that about an extra 128 ms is required on average to solve this problem. These RT results should be replicated, but the consistency and very high levels of significance of the RT comparisons indicate that there is a real sex difference here.

It is now established that during childhood and adolescence the volume of white matter (WM: nerve axons, myelin around the axons, and glial cells) in the brain steadily increases. In males this volume very probably increases faster than in females (De Bellis et al., 2001; Giedd et al., 1999). This increase in WM could be due to increased myelination, increased axon size, glial proliferation, or a combination of these (De Bellis et al., 2001). Because both increased myelination and increased axon size lead to faster nerve conduction (Koester, 1991), these WM findings support our results of faster brain NCV in males than in females. They may also support our finding of a possible sex difference in age-NCV correlation (the *one*-tailed probability—justified here because of prior expectation from the above WM findings—for this is 0.031).

There is a further interest in using the optic radiation to obtain brain NCV estimates: the optic radiation, which is heavily myelinated (Bürgel, et al., 1999), may be typical of the subcortical WM in general because the mean diameter of the myelinated fibers in brain WM is also very small, about 1 μm (Tang, Nyengaard, Pakkenberg & Gundersen, 1997). Our NCV estimates may therefore be representative of brain WM NCV in general and, because nerve axons in the WM connect neurons both within and between different regions of the cerebral cortex, these estimates should be relevant for understanding the rates of cognitive processes in general.

It may also be relevant here that the one published study on brain NCV, in male university students (Reed & Jensen, 1992), found a correlation of +0.26 ($P = 0.002$) between visual pathway NCV and a non-verbal measure of intelligence (Raven). Correcting for restricted intelligence range (but not for test ceiling or attenuation) gave a correlation of +0.37. Support for this correlation comes from studies of mentally retarded (phenylketonuric) children using a similar visually evoked technique. They found significantly increased mean P100 latencies relative to age-matched controls (Korinthenberg, Ullrich & Füllenkemper, 1988; Landi et al., 1987); these increased latencies correspond to decreased visual pathway NCVs in these retarded children.

In conclusion, two independent approaches, using nerve pathway measurements and reaction time measurements, strongly agree in showing that in normal young adults, males have a faster brain NCV than do females. This sex difference may be explained by sex differences in the maturation of the white matter in the brain.

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