

Sexual dimorphism in tendon reflexes and nerve conduction velocity: a systematic review

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Received 29 July 2021; accepted 5 January 2022

Summary. Spinal reflexes are the pillars of the motor system's organization. The assessment of the spinal cord reflexes is an exploratory routine in neurological and clinical practice, providing valuable, real-time information about the state of our nervous system, in health as well as in illness. The influence of sex in some neurological diseases is largely recognized. Nevertheless, we noted a shortage of clinical or research studies recording the differences in spinal cord reflexes. Thus, we reviewed the existing sex-disaggregated data literature on spinal cord reflexes. Based on the studies reporting sex-disaggregated data, we can conclude that there is a sex dimorphism in the knee jerk reflex, since there is a shorter reflex latency in females than in males.

Keywords. Sex, neurology, conduction velocity, reflex, gender.

Introduction

A reflex is a stereotyped and involuntary response to sensitive (somatic or visceral) input, usually throughout simple neuronal circuits. Although reflexes can be modulated upon upper cerebral centers, the integration center of the response to the stimulus is located either in the brainstem or in the spinal cord. Broadly speaking, reflexes are relevant for survival, as muscle tone, posture, equilibrium as well as a vast array of visceral functions are carried out thanks to reflex circuits.¹

In clinical practice, the study of reflexes is extraordinarily significant: depending on their alteration or absence, damage to the underlying circuits can be established. Thus, clinical neurophysiology employs certain parameters associated with reflexes as diagnostic variables. In this scenario, conduction velocity as well as reflex latency measurements are non-invasive variables that help the diagnosis of neuropathies, as well as their follow-up.^{2,3}

Sex-specific differences in the peripheral nervous system have been previously described not only in humans,⁴⁻⁶ but also in rats^{7,8} and mice.⁹ This leads to the conclusion that the clinical practice values considered normal in nerve conduction velocity (NCV) and latency in males will be necessarily different from those of females, and may change in subjects undergoing hormonal treatment.

Our hypothesis is that there is a sexual dimorphism for NCV and somatic reflex latency in humans. However, at present this topic is very poorly documented, and it has not been determined whether the results reported so far are conclusively in accordance with the existence of sexual dimorphism. Therefore, the objective of this review is to establish whether there is consensus in the studies carried out to date in order to deduce the existence of sex-specific differences with respect to both variables. This would be greatly valuable, since it would allow to then suggest which physiological factors lead to sexual dimorphism and to eliminate the diagnostic bias in clinical practice.

Methods

A systematic review of the scientific literature related to the existence of a possible sexual dimorphism in the conduction of information through the nervous pathways has been carried out. The review was performed between October 2019 and May 2021.

A main search was carried out in the PubMed biomedical literature database, which was completed using the Europe PMC and Google Scholar databases. Both national and international documents were searched, applying the keywords 'gender', 'sex', 'reflex' and 'difference' in combination with 'motor nerve conduction velocity' ('MNCV') and 'latency'. The search was performed in English and Spanish only, and no age limit was specified, but an attempt was made to select the most recent studies. In addition, the bibliography sections corresponding to the studies found were reviewed –selecting those that could serve as support – and were subsequently searched in the PubMed database.

The main requisite for the inclusion of the studies in this review was that they reported – by sex – neurophysiological characteristics that could influence latency or MNCV. The exclusion criterion selected was that no sex-specific comparisons were made with respect to latency or MNCV.

Between scientific studies and systematic reviews, 180 results were found whose titles suggested a relationship with the purpose of this review. The selection of these

articles was made by reviewing the abstracts, in order to determine if they met the inclusion criteria.

The review was carried out on 22 scientific studies, four of which were discarded because they found sex differences oriented to muscle physiology only, which meant they did not fit the purpose of this review. In the end, the review consisted of 18 scientific studies.

The analysis of the selected studies was structured by subdividing the anatomical region of the upper limb and head together, and the anatomical region of the lower limb. We found two studies related to the autonomic nervous system (ANS), that reported sex-specific differences and that were included separately from the previous ones. For all of them, subgroups were created, according to the nerve studied in each reflex.

A table was created, which summarized the following: the type of reflex, the intervening nerve, sex and ages of the subjects, measurement technique, sex-disaggregated latency values, MNCV values categorized by sex, dimorphism in the values obtained, and statistical significance of the results. For all the articles included in the table, the name of the author(s) was linked to the abstract published in the PubMed database, except for one, whose abstract was linked to that published in Europe PMC. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) scale was used to carry out this review (figure 1).¹⁰

Anatomical region of the lower limb

Six studies measuring latencies and MNCV in reflexes and nerves of the lower limb were selected. In all of them, both parameters were measured by sEMG, and the results were disaggregated by sex. In five studies, data was taken from a sample of both sexes, whereas Singh et al.¹¹ took only a female sample. The studies focused on investigating latencies and/or MNCV on the femoral, sural, peroneal, tibial, median plantar, lateral and calcaneal nerves (see Table 1 for a detailed description).

Femoral nerve

Three studies measured the latencies of the patellar reflex on the femoral nerve in subjects aged 18-64. For all of them, 1-to-4 ms shorter latency values were found in females than in males – this difference being statistically significant.^{6,12,13} In addition, the study by Tindell and Smith⁶ also measured the conduction velocity, which yielded results of 52.5 ± 1.5 m/s in females, versus 47.6 ± 1.3 m/s in males.

In all cases, linear regression and correlation analyses were performed in order to determine if the latency difference was caused by any difference in height or thigh length between the sexes. Two of them showed affirmative results.^{6,12} The Vickery and Smith study¹³ reported

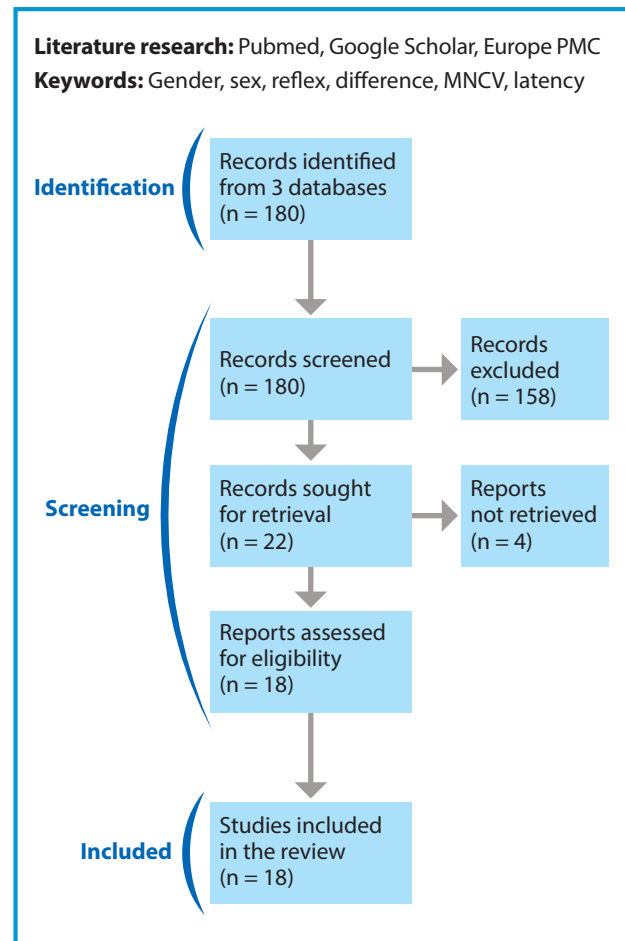


Figure 1. PRISMA flow diagram of the article search and selection process.

that a correlation with height had been found for a group of both sexes, but not for groups of the same sex. However, in the study by Tindell and Smith,⁶ it was also reported that for any value of thigh length men always present a longer latency, which highlights a contradiction with the correlation results between latency and height from the same study.

Rest of nerves of the lower limb

Mylius et al.¹⁴ measured the latency of the flexor nociceptive reflex on the sural nerve on a sample aged between 20 and 40. The results showed a shorter latency in males (96.8 ± 17.6 ms) than in females (95.2 ± 16.5 ms). Nevertheless, statistical significance values were not reported.

In the study by Cinar et al.,¹⁵ the latency and MNCV of the tibial, median plantar, lateral, calcaneal and sural nerves were measured in a sample aged between 20 and 50. Although the values obtained for either of the two parameters were not shown, it was reported that in none of the cases did the results reach the threshold of statistical significance. Peroneal nerve MNCV was also measured in two groups of postmenopausal women, one

Table 1. Summary of the information analyzed in each of the reviewed studies, grouped in descending order of anatomical limb and nerve involved and arranged chronologically

| Author/s | Reflex | Nerve | Sex/age range (years) | Technique | Latencies (ms) | MNCV (m/s) | Dimorphism | Statistical significance |
|--|----------------------|--|-----------------------|-----------------------|------------------------------|------------------------------|--------------------------------|--------------------------|
| Kossioni & Karkazis (1994) ²⁸ | Masseter | Trigeminal | ♂♀ 21-26 | sEMG | ♀ 5.75±1.09 ♂ 6.14±1.28 | - | Yes ♀<♂ | Yes |
| Peddireddy et al. (2006) ²⁹ | Masseter | Trigeminal | ♂♀ 24-28 | sEMG | ♀ 8.3±0.7 ♂ 8.4±0.7 | - | No | No |
| Kiziltan et al. (2010) ³⁰ | Masseter inhibitory | Trigeminal | ♂♀ 19-65 | sEMG | ♀ 52.8±9.4 ♂ 52.1±6.6 (1) | - | No | No |
| Kiziltan & Gündüz (2020) ³¹ | Trigeminal -cervical | Trigeminal | ♂♀ 18-75 | sEMG | * | - | No | No |
| Peddireddy et al. (2006) ²⁹ | Blink | Trigeminal | ♂♀ 24-28 | sEMG | ♀ 39.4±3.5 ♂ 36.4±3.5 (2) | - | No | No |
| Kiziltan et al. (2010) ³⁰ | Blink | Trigeminal | ♂♀ 19-65 | sEMG | ♀ 31.5±2.5 ♂ 31.2±2.5 (3) | - | No | - |
| Kofler et al. (2013) ³² | Blink | Trigeminal | ♂♀ 27-54 | sEMG | ♀ 32.3±3.8 ♂ 33.0±3.8 (4) | - | No | No |
| Kommalage & Gunawardena (2013) ³³ | | Ulnar | ♂♀ 11-96 | sEMG | - | ♀ 56.1±4.93 ♂ 54.04±5.00 | Yes ♀>♂ | Yes |
| Alemdar (2014) ³⁴ | | Median-ulnar | ♂♀ 16-68 | sEMG | - | ♀ 58.3±5.8 ♂ 57.7±5.4 (5) | No | No |
| Singh et al. (2016) ¹¹ | | Median-ulnar | ♀ Postmenopausal | sEMG | - | * | Yes | Yes |
| Tan U (1991) ³⁵ | Hoffman | Piramidal tract | ♂♀ 18-21 | sEMG | ♀ 29.9±1.3 ♂ 31.5±1.5 | - | Yes ♀<♂ | - |
| Miller et al. (2010) ⁴ | Paraspinal | Cutaneous (several) | ♂♀ 19-35 | sEMG | ♀ 48.8±3.0 ♂ 60.0±3.2 | - | Yes ♀<♂ | Yes |
| Sajadi et al. (2014) ¹⁶ | | Cutaneous antebrachial posterior | ♂♀ 22-75 | sEMG | - | ♀ 58.64±9.31 ♂ 56.90±5.46 | No | No |
| Alisaukiene et al. (2007) ¹² | Knee-jerk | Femoral | ♂♀ 18-64 | sEMG | ♀ 20.9±1.58 ♂ 22.7±1.92 | - | Yes ♀<♂ | Yes |
| Vickery & Smith (2012) ¹³ | Knee-jerk | Femoral | ♂♀ 20-22 | sEMG | ♀ 17±0.23 ♂ 21±0.3 | - | Yes ♀<♂ | Yes |
| Tindell & Smith (2017) ⁶ | Knee-jerk | Femoral | ♂♀ 19-21 | sEMG | ♀ 22.0±0.2 ♂ 24.1±0.22 | ♀ 52.4±1.5 ♂ 47.6±1.3 | Latency Yes ♀<♂ NCV Yes ♀>♂ | Yes |
| Mylius et al. (2005) ¹⁴ | Flexor nociceptive | Sural | ♂♀ 20-40 | sEMG | ♀ 96.8±17.6 ♂ 95.2±16.5 | - | Yes ♀>♂ | |
| Cinar et al. (2013) ¹⁵ | | Tibial Median plantar Lateral Calcaneous Sural | ♂♀ 20-50 | sEMG | * | * | No | No |
| Singh et al. (2016) ¹¹ | | Peroneal | ♀ Postmenopausal | sEMG | - | * | Yes | Yes |
| Fan et al. (2009) ³⁶ | Pupillary | Motor ocular (III) ANS | ♂♀ 18-22 | Pupilogram | * | - | No | No |
| De Campos et al. (2014) ²² | | Laringeal ANS | ♂♀ 70-76 | Histological sections | - | - | Yes, g-ratio ♀<♂ | Yes |

Latency and MNCV data represented as mean ± standard deviation.

- indicates an unmeasured parameter; * indicates those results not reported for a measured parameter.

ANS, autonomic nervous system; sEMG, surface electromyography; (1), latencies of the left SP2 response with electrical stimulation; (2), R2 response initiation latencies; (3), latencies of the R2 response on the left side; (4), latencies of the unconditioned R2 response; (5), MNCV of the median nerve.

with peripheral neuropathy and one without. In a linear regression analysis, the significantly different results obtained between the two groups were positively related to the level of serum estrogen, more abundant in the subjects without neuropathy.¹¹

Discussion

Factors that can explain sexual dimorphism

The results obtained indicate that there clearly is a difference between the sexes with regard to the latency of the patellar reflex on the femoral nerve; however, this is not a result that can be extrapolated to the rest of the nerves of the lower anatomical limb.

Given that both MNCV and pathway length intervene in latency, it would be plausible to infer that in males these variables are higher than in females, given a greater height and thigh length. This is because the conduction of the action potential in the patellar reflex occurs along the trunk of the femoral nerve, whose length is the same as that of the thigh¹³. The results of Alisauškiene et al.¹² and Tindell and Smith⁶ support this hypothesis. However, Vickery et al.¹³ showed that within groups of the same sex there was no correlation between latency and height. They associated positive results with the combination of both sexes – combining the data for women and men masks the possible effects of sex on latency, by associating them with height. However, the study by Tindell and Smith⁶ reported that for any value of thigh length, men always present a longer latency than women. This supports height as a confounding variable, and yet it is inconsistent with the results previously produced in the same study. Another explanation may be the differences in body mass index (BMI), which is inversely correlated with the MNCV of the posterior tibial nerves, distal branches¹⁵ and some sensory nerves.¹⁶ In this instance, Fanin et al.¹⁷ carried out an extensive morphometric study on limb-girdle muscular dystrophies, which showed sex dimorphism. These differences in BMI and/or muscle mass should be considered in sex-aggregated studies also.

It is interesting to note that Nowak-Szczepanska and Koziel¹⁸ found a sexual dimorphism in the length of teenagers' forearms, but not in the leg length. Surprisingly, Zhang and Li¹⁹ found significant differences in the sitting height to subischial length proportion, being larger in adult females than in males. Among the neuroanatomical characteristics that we know determine, MNCV is the diameter of the axon, whose greater cross-sectional area is associated with a larger size of the soma or cell body.⁶ It is known that the soma area of the alpha motor neurons of the L3 lumbar region, with which the femoral nerve is associated, is larger in men than in women.^{6,13} This leads to think that, by having a larger

soma, males should present a higher MNCV than women and, therefore, a lower latency of the knee jerk reflex. However, this hypothesis is not consistent with the results found, in which MNCV in women is significantly faster than in men.^{6,13} Nevertheless, the patellar reflex can also be affected by unique conditions, such as L5 root monoradiculopathy. This monoradiculopathy may generate a change in the patellar reflex, slowing it down or eliminating it completely.²⁰ This may mask the expected result of increased MNCV in men, due to the larger size of the soma at the L3 root, since a simultaneous L5 root monoradiculopathy may also be occurring, thereby changing the levels compared to women. This result can also be explained by the "principle of size recruitment", according to which smaller neurons are recruited earlier, since they present a greater electrical resistance and reach the threshold earlier.^{1,6,13} Since males have alpha motor neurons with a greater cross-sectional area than females, there is a synaptic delay between the afferent and efferent neurons, that translates into a delay in their latency.^{6,13} This is consistent with the results of Nishikawa et al.,²¹ who concluded that there was a sexual dimorphism for the recruitment of motor units.

In addition to the size of the alpha motor neurons, myelination of the axons can also be considered as a cause of sexual dimorphism in the lower limb. It could be assumed that women present a higher g-ratio than men but, once again, this hypothesis does not match the previous results on g-ratio between the sexes, which has been shown to be higher in males than in females.²² Another factor that implies an increase in MNCV is the greater distance between the Ranvier nodes,²³ so it would be possible for women to present a greater internodal distance than men.^{6,13}

In the same way, we can consider the density of the voltage-regulated Na⁺/K⁺ channels present in the Ranvier nodes.^{6,13} Through these channels, the generation and conduction of the action potential is allowed.¹ Thus, fewer channels or different activation properties (such as the need for a higher concentration of Na⁺ ions to activate them) could cause differences in the transmission of the impulse, and therefore in reflex latency between the sexes.

In addition to the neuroanatomical features, a positive correlation has also been reported between the estrogen concentration and MNCV of the peroneal nerve.¹¹ Given the difference in the concentration of hormones between the sexes, it would be plausible to think that this is a factor intervening in sexual dimorphism for latency and MNCV also in the lower limb.

According to the information found, it seems that sex hormones are the factor with the greatest probability of influencing sex differences in nerve conduction. Estrogens, such as 17 β -estradiol (E2), are the hormones that

have been most investigated so far in terms of nerve conduction, due to their effects on the nervous system, such as neuronal excitability or neuroprotection.²⁴ An evident effect has been determined in all scientific studies in which it has been considered as a variable. However, there are other hormones that could have a significant influence, such as androgens. Androgens are sex steroids which trigger important functions in humans.²⁵ Because one of the main functions of androgens is the production of male sexual characteristics, it can be inferred that higher-than-normal levels of androgens in women would lead to a masculinization of nerve conduction parameters, that is, a delay in MNCV and an increase in latency; a male phenotype would develop for MNCV. Similarly, this can occur in cases of androgen insensitivity syndrome, where men have a female MNCV phenotype.²⁶ In the case of women, the natural overproduction of androgens can be due to congenital adrenal hyperplasia, that develops while in the womb, or from polycystic ovary syndrome, that develops after childbirth.

Congenital adrenal hyperplasia is a genetic disorder of the adrenal glands that is directly related to androgen overproduction, as is polycystic ovary syndrome, which occurs when the ovaries produce more male hormones than normal.^{6,27} In addition to finding androgen overproduction in women with congenital adrenal hyperplasia and polycystic ovary syndrome, the cases of women undergoing treatments with these hormones for sex change could also be considered. However, this should undergo separate considerations, since the increase in androgens would not be produced by the body itself, and therefore may not affect the nerve conduction parameters in the same way. Thus, through research on these hormones, the range of the possible origins of sex-specific differences in nerve conduction could be narrowed down.

Key messages

- Although based on scarce data, all of the articles reporting knee jerk latencies found a significant sexual dimorphism in knee jerk reflex latency.
- A statistical correlation has been reported between height, limb length, spinal cord size and neural pathway length and nerve conduction velocity and/or reflex latency. Nevertheless, a detailed cause-effect relationship of these variables has not been studied yet, as there are some controversial data on this issue.
- Possibly, gonadal hormone levels might account for sex-specific differences.

Conclusions

The results of this review confirm that sex has an influence on the development of reflexes and the conduction of nerve stimuli on certain nerves.

Sexual dimorphism cannot be concluded for the functioning of the reflex pathways on the trigeminal nerve. The results indicate that there are slight differences between the sexes (in the case of the masseter reflex with a tendency to a shorter latency for women), but they were not sufficiently consistent to consider them as an effect of sex.

We found clear evidence of the existence of sexual dimorphism in both latency and MNCV of the femoral nerve in the patellar reflex. Women always have shorter latencies and higher driving speeds than men.

There is insufficient data to establish with certainty a sexual dimorphism in the rest of the nerves of the lower limb, where not even a trend can be reported, due to a lack of studies. Nor can we establish sexual dimorphism on the autonomic nervous system, because of a lack of data.

The causes of these differences are not clear, although they are likely closely related to sex hormones, since most of the studies reviewed included this factor as a limitation, and those who analyzed it concluded that there was indeed a correlation.

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Author contribution statement: SCD performed the database search and compiled the table. FS wrote the article and search additional references for the discussion and introduction. SCD also participated in the final version of the article.

Conflict of interest statement: the Authors declare no conflicts of interest.

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