Vibrotactile perception depends on cognition not just peripheral nerve integrity: a cross-sectional study

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ABSTRACT

Background: Vibration perception is often considered a peripheral nerve and dorsal column function, without considering the role of cognition. The current study tested cognition's role in vibrotactile perception thresholds (VPT).

Methods: We recruited cases with mild-moderate dementia or mild cognitive impairment thought to reflect probable Alzheimer's pathology (AD/MCI group), and controls without memory concerns (all participants >50 years). Polyneuropathy, B12 deficiency, diabetes, or other conditions associated with cognitive impairment were exclusionary criteria. Participants underwent cognitive evaluation with the Self-Administered Gerocognitive Examination (SAGE), standardized nerve conduction studies, and quantitative VPT testing. Demographic and medical history were obtained through interviews and chart review. We constructed linear regression models to test whether poor cognition correlates with VPT.

Results: Nineteen AD/MCI participants (age 71.5±8.9, 47.4% female) and fourteen controls (age 67.4±9.3, 78.6% female) did not differ in age or gender. Univariate predictors of poor/increased mean VPT (all p-values <0.10) were age, AD/MCI, SAGE score, sural sensory nerve action potential (SNAP) amplitude <5 microvolts, yearly income <$50,000, history of vascular disease, and peroneal motor and sural conduction velocity (CV). SAGE score (standardized β=-0.38, p<0.01); sural SNAP amplitude (β=0.51, p<0.001); peroneal motor CV (β=-0.37, p<0.01), history of vascular disease (β=0.27, p=0.03), and female gender (β=0.22, p=0.10) remained independently associated with VPT in multivariable linear regression analysis (backward modeling; removal criteria p>0.10; model adjusted R^2=0.66; p<0.001).

Conclusions: Poor cognition is associated with worsened VPT. Neurologists should consider cognition when using sensory perception to assess peripheral nerve integrity, both for research and during a traditional neurologic examination.

Introduction

The assessment of vibrotactile perception (VP) is a canonical component of the neurological examination, used to interrogate the dorsal column-medial lemniscus (DCML) afferent pathway. Impaired VP results from interruption anywhere along the DCML's caudal-rostral extent, including "disease of multiple peripheral nerves, [the DCML], and thalamus."[1] The role of cortical function in VP is less widely appreciated. It is conceptually obvious that conscious stimulus detection must be perceived in the cortex, but few studies have formally tested cognition's role in somatosensation. Deficits in other senses have been linked to poor cognition. Poorer olfactory discrimination has long been recognized as a risk factor for cognitive impairment in both Parkinson's disease and Alzheimer's disease.[2] Poorer somatosensory and auditory perception have also been preliminarily linked to cognitive decline,[3] though this has not been well-studied. If deficient VP can be linked to poor cognition, VP testing could be used to identify those at risk of future cognitive decline or as a biomarker to track progression. In addition, since VP testing (as part of the neurological exam) is widely used for clinical localization, understanding cognition's role is crucial to correctly interpreting the exam.

In this cross-sectional pilot study, we tested the hypothesis that cognition is associated with VP thresholds (VPT).

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the Dartmouth Committee for the Protection of Human Participants (STUDY#00029795). All participants provided written informed consent prior to participation.

From March 2017 to May 2019 we recruited a convenience sample from the Dartmouth-Hitchcock Neurology clinic. Cases were referred by their primary cognitive/behavioral neurologists if they were age ≥50; diagnosed with amnestic mild cognitive impairment, mild-to-moderate dementia, or major neurocognitive disorder; and Alzheimer's pathology was considered the most probable etiology. "AD/MCI" cases required glucose and B12 screening within 3 months and native English proficiency (for cognitive testing). Excluded were participants with B12 deficiency or diabetes; cognitive impairment from another condition (e.g. vascular dementia, epilepsy, Parkinson's disease); or known neuropathy. Controls were spouses of cases or members of our department. Controls were excluded for diagnoses of neuropathy; cognitive impairment or subjective concerns; B12 deficiency; or diabetes.

We calculated *a priori* that 32 total participants (16 cases and 16 controls) would be required to achieve adequate power, based on a clinically significant difference between groups in mean VPT of 25% (100 units versus 75 units), sampling ratio of 1, standard deviation of 40 units, $\beta = 0.20$ and $\alpha = 0.05$.

All participants underwent structured interviews abstracting information regarding demographics; clinical history (e.g. vascular risks, axial or sciatic-type pain; sensory symptoms; chemotherapy exposure); family history (e.g. neuropathy, dementia); Geriatric Depression Score[4]; and the Self-Administered Gerocognitive Examination (SAGE).[5] SAGE assesses multiple cognitive domains; correlates highly with neuropsychologic testing; and is both sensitive and specific for diagnosing MCI and early dementia.[5] Scores range from 0-22, with SAGE≥17 considered normal.

After limb warming to ≥30.0° Celsius, participants underwent nerve conduction studies (NCS) with our lab's trained technicians using a Natus® Nicolet VikingQuest system according to the techniques described by Preston and Shapiro,[6] including the right sural, peroneal motor, tibial motor, radial sensory, and ulnar motor nerves. Care was taken to ensure supramaximal stimulation and optimization of response according to defined landmarks and measured distances. Norms were derived from the Dartmouth-Hitchcock EMG clinical laboratory. Quantitative VPT was tested using a Vibratron II system (Physitemp Instruments, Inc., Clifton, NJ). After instructions, participants did a practice trial with finger perception. Then, seated participants placed the plantar surface of the bare right great toe (warmed >30.0°C) on the device's vibrating surface. Vibration intensity was slowly increased from 0 vibration units (VU) in 0.4 VU increments until participant's reported perception. After two practice trials, 5 additional trials were conducted, and results were averaged ("mean VPT") for final analysis. If the inter-trial variance was >20%, the procedure was repeated. Participants who did not detect even the most perceptible stimulus (210 VU) were assigned a VPT of 230 VU.

Clinical record forms were entered into a secure REDCap database. SPSS v25.0 (IBM Corp., Armonk, NY) was used for all analyses. We first compared independent variables with VPT using Pearson's *r* for continuous data, and a student's *t*-test for binary variables. We then constructed multivariable linear regression models with VPT as the outcome, entering all variables associated with VPT in bivariate analysis along with gender. We employed "backward" regression modeling (removal criteria $p>0.10$), which eliminated collinearity (e.g. between AD/MCI diagnosis and SAGE score) and produced normally distributed residuals.

Data Availability

Anonymized data is maintained securely and sharable for 10 years to qualified investigators with ethics approval.

Results

19 cases and 14 controls were enrolled. All participants completed the study. Characteristics of the sample are shown in *Table 1*. AD/MCI diagnosis closely mirrored low SAGE: 16/17 participants with SAGE≤16 had clinical AD/MCI, versus 3/16 participants with SAGE≥17 ($p<0.001$, Fisher's Exact). Although all participants saw a doctor regularly without a neuropathy diagnosis, 17/33 participants (51.5%) had at least one abnormally low amplitude SNAP or CMAP (sural <5 microvolts; distal peroneal <2.5 millivolts; distal tibial <3.5 millivolts). Age, AD/MCI diagnosis, lower SAGE, history of vascular disease, income (<$50,000/year), low sural amplitude, sural conduction velocity (CV), and peroneal motor CV were all associated with VPT ($p<0.10$): *Table 1* contains results from univariate analysis showing factors associated with VPT.

Starting with gender and all factors related to VPT in univariate analysis (except income; see below), age, AD/MCI diagnosis, and sural CV were all removed from the final regression equation. The following variables were independently associated with VPT and retained in the final model ($F(5,26)=13.1$; R^2(adjusted)=0.66, $p<0.001$): SAGE; low sural amplitude; female gender; vascular disease history; and peroneal CV (*Table 2*). In sensitivity analysis, substituting individual visuospatially-oriented SAGE questions (i.e. 7 and 8) for total SAGE produced similar results.

One participant had missing income data, so we conducted sensitivity analyses to ensure the data's fidelity: excluding that participant, including that participant with imputed income, and excluding income. Income dropped out of all models so was omitted in the final analysis (above). The analysis was repeated after logarithmically transforming VPT due to a slight right skew and ceiling. SAGE remained independently correlated [β(standardized)= -0.28; $p=0.02$;($F(3,28)=13.8$; R^2(adjusted)=0.55, $p<0.001$)].

Table 1. Characteristics of the sample and results from univariate analysis showing factors associated with Vibrotactile Perception Threshold (VPT), n = 33

Variable	median (IQR)[a], or n (%)	Difference in VPT mean*, or correlation (Pearson's r)	*p-value*
Age	68.0 (63.0-76.5)	(0.44)	0.01
Female gender	20 (60.6)	0.16	0.46
Highest educational attainment ≤ high school	12 (36.4)	0.88	0.72
Yearly income less than $50,000[b]	14 (43.8)	4.20	0.08
Diagnosis of probable AD or aMCI[c] (case)	19 (57.6)	4.56	0.02
Medical conditions			
history of vascular disease[d]	8 (24.2)	4.12	0.09
hypertension[e]	9 (27.3)	- 0.93	0.72
dyslipidemia[e]	12 (36.4)	- 0.89	0.70
self-reported history of tobacco use	16 (48.5)	- 0.01	1.00
self-reported history of back pain	18 (54.5)	- 0.60	1.00
self-reported history of radicular back pain	5 (15.2)	- 1.51	0.48
self-reported history of neck pain	7 (21.2)	- 0.15	0.95
self-reported history of numb feet	6 (18.2)	3.34	0.34
self-reported family history of neuropathy	4 (12.1)	2.10	0.67
self-reported family history of dementia	15 (45.5)	1.33	0.55
Average VPT (VPT units)	6.7 (3.7-11.7)	-	-
Geriatric Depression Score	1 (0-2)	(0.21)	0.24
Self-Administered Gerocognitive Examination (SAGE) score	16 (12-21)	-(0.50)	< 0.01
Low SAGE score (≤ 16)	17 (51.5)	4.38	0.04
Nerve conduction results[f]			
Low distal tibial CMAP (< 3.5 millivolts)	7 (21.2)	5.09	0.18
Low distal peroneal CMAP (< 2.5 millivolts)	7 (21.2)	3.45	0.29
Low sural SNAP (< 5 microvolts)	12 (36.4)	7.18	< 0.01
Absent sural SNAP	4 (12.1)	6.28	0.16
Sural SNAP amplitude (microvolts)	6.5 (4.7-9.25)	(- 0.27)	0.13
Sural SNAP conduction velocity (m/s)	47.1 (41.4-51.2)	(- 0.52)	< 0.01
Distal peroneal CMAP amplitude (millivolts)	4.2 (2.8-6.2)	(- 0.26)	0.14
Distal tibial CMAP amplitude (millivolts)	8.1 (5.6-11.1)	(- 0.14)	0.43
Peroneal conduction velocity (m/s)	44.1 (42.2-46.6)	(- 0.33)	0.06

[a] IQR = interquartile range; SNAP = sensory nerve action potential amplitude; CMAP = compound motor action potential;

* Difference in means, two-tailed t-test for Equality of Means, equal variances not assumed; [b] n = 32

[c] Cases were all diagnosed by their primary neurologist with cognitive impairment or dementia, thought to be due to Alzheimer's pathology

[d] Vascular diseases include cardiovascular, cerebrovascular, or peripheral vascular disease

[e] Hypertension and dyslipidemia = those who identified this by history, or were on medications aimed at treating these conditions

Table 2. Factors independently associated with increasing vibrotactile perception threshold (VPT)*

Variable	*p-value*	Standardized Beta*
SAGE score	< 0.01	- 0.38
Sural SNAP amplitude < 5 microvolts	< 0.001	0.51
Peroneal motor conduction velocity in the leg (m/s)	< 0.01	- 0.37
History of vascular disease	0.03	0.27
Female gender	0.10	0.22

*results from backwards linear regression (criteria for removal $p > 0.10$); n=33, with the following factors entered for consideration: diagnosis of probable Alzheimer's disease or mild cognitive impairment thought like to be due to Alzheimer's disease (AD/MCI diagnosis); sural lower leg conduction velocity (CV); female gender; age; history of vascular disease (cerebrovascular, cardiovascular, or peripheral vascular); peroneal motor CV stimulating below the fibular head and recording from extensor digitorum brevis; sural sensory nerve action potential amplitude < 5 microvolts; total Self-Administered Gerocognitive Exam (SAGE) score

**increase in VPT (vibration units) with either a) the presence of the variable (binary variables), or b) one unit increase of the variable (continuous variables)

Discussion

This study's central finding is that cognition is independently and robustly associated with vibrotactile perception, adjusting for age, gender, and peripheral nerve parameters (i.e. axonal integrity, CV). Several important corollaries follow. First, the clinical use of VP to test peripheral nerves must be filtered through the understanding that deficits localize anywhere along the DCML, and even as rostral as the cortex. Normal VP may suggest normal cognition, while impaired VP may warrant investigation. In the absence of peripheral neuropathy, lumbosacral radiculopathy, or cervical myelopathy, poor VP on neurologic exam may warrant further cognitive evaluation. Second, these results underscore that VP testing is not sufficient to establish nerve fiber loss. In other words, impaired VP has a wider differential than peripheral nerve fiber loss, and research studies that equate poor VPT with peripheral nerve dysfunction make an unwarranted assumption.[3,7] Impaired VPT can reflect peripheral neuropathy and afferent failure, but cognition and spinal conduction also influence perception. The common practice of interpreting poor tuning fork perception as a demonstration of large fiber afferent or DCML damage may be too simplistic. Similarly, the subtly decreased vibratory perception sometimes observed in the elderly may reflect cognitive impairment, not subclinical neuropathy or cervical spondylitic myelopathy. Further study is warranted.

This study has several strengths. This is the first study to examine the relationship between cognition and VPT utilizing comprehensive NCS and a multi-domain cognitive assessment. Prior studies either did not test sensory nerves[3] or used a limited cognitive battery.[8] We also screened out individuals with neuropathy or risk factors (e.g. diabetes) and adjusted for peripheral nerve health (i.e. axonal integrity, CV). This design strengthens the conclusion that increased VPT is due to higher-order deficits, not subclinical neuropathy, and parallels findings from other studies suggesting poor sensory perception is a cognitive deficit.[2,3]

There are also limitations. The cross-sectional design precludes causative attribution; while cognitive impairment may contribute to poor VP, this association may reflect an unmeasured shared risk factor. In that case, VPT might still prove to be a useful biomarker for predicting or tracking AD/MCI; future studies should test this. Second, this pilot study was small and nonrandom. Replication using age and sex-matched controls and a large sample, or a prospective design, is warranted. However, the effect magnitude supports the conclusions. Third, AD/MCI diagnosis relied on expert opinion, not pathology, and AD and MCI were conflated. However, the finding that VP associates with cognitive impairment does not depend on the pathologic etiology and merely reflects poor sensory perceptive integration.

Conclusions

In summary, poor cognition is associated with impaired VPT. Clinicians and researchers should consider cognition's role when using sensory perception to assess peripheral nerve integrity.

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content is solely the responsibility of the author(s) and does not necessarily represent the official views of the NIH. The funders were not involved in the study. In addition, study data were collected and managed using REDCap electronic data capture tools hosted at Dartmouth.

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Disclosures
Drs. Robbins, Bujarski, Stark, Stommel, and Lawson report no disclosures relevant to the manuscript.
Mr. Palladino, Ms. Bursey, and Mr. Mason report no disclosures relevant to the manuscript.

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Appendix 1.

Author	Location	Contribution
Nathaniel M. Robbins MD	Geisel School of Medicine at Dartmouth-Hitchcock Hanover, NH	Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content
Kris A. Bujarski MD	Geisel School of Medicine at Dartmouth-Hitchcock Hanover, NH	Interpreted the data; contributed study participants; revised the manuscript for intellectual content
Aleksandra C. Stark MD	Geisel School of Medicine at Dartmouth-Hitchcock Hanover, NH	Major role in the acquisition of data; contributed study participants; revised the manuscript for intellectual content
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Elijah W. Stommel MD, PhD	Geisel School of Medicine at Dartmouth-Hitchcock Hanover, NH	Revised the manuscript for intellectual content
Victoria H. Lawson MD	Geisel School of Medicine at Dartmouth-Hitchcock Hanover, NH	Design and conceptualized study; interpreted the data; revised the manuscript for intellectual content