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Paper:

Hanley, C., Burianová, H. & Tommerdahl, M. (2019). Towards Establishing Age-Related Cortical Plasticity on the Basis of Somatosensation. *Neuroscience*
<http://dx.doi.org/10.1016/j.neuroscience.2019.01.023>

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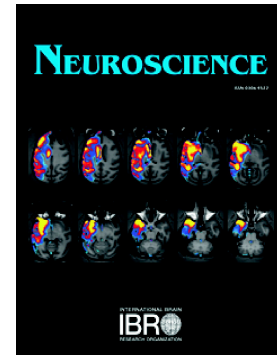
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Accepted Manuscript

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PII: S0306-4522(19)30043-0

DOI: <https://doi.org/10.1016/j.neuroscience.2019.01.023>

Reference: NSC 18849

To appear in: *Neuroscience*

Received date: 17 August 2018

Accepted date: 16 January 2019

Please cite this article as: C.J. Hanley, H. Burianová and M. Tommerdahl, Towards Establishing Age-Related Cortical Plasticity on the Basis of Somatosensation, *Neuroscience*, <https://doi.org/10.1016/j.neuroscience.2019.01.023>

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Towards establishing age-related cortical plasticity on the basis of somatosensation.

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Abstract

Age-related somatosensory processing appears to remain intact where tasks engage centrally- as opposed to peripherally-mediated mechanisms. This distinction suggests that insight into alterations in neural plasticity could be derived via metrics of vibrotactile performance. Such an approach could be used to support the early detection of global changes in brain health but current evidence is limited. Knowledge of the precise conditions in which older adults are expected to sustain somatosensory performance is largely unknown. For this purpose, the study aimed to characterise age-related performance on tactile detection and discrimination-based tests. Accordingly, a group of young and older adult participants took part in simple reaction time and amplitude discrimination tasks. Participants' ability to distinguish between stimuli on the basis of amplitude was assessed with and without dual-site adaptation, which has been proposed to refine cortical responses and improve behavioural performance. The results show that while older adults exhibited significantly prolonged ($p < .001$, $d = 1.116$) and more variable ($p = .022$, $d = .578$) information processing speed compared to young adults, they were able to achieve similar scores in baseline discrimination ($p = .179$, $d = .336$). We also report, for the first time, that older adults displayed similar performance improvements to young adults, under conditions of dual-site adaptation ($p = .948$, $d = .016$). The findings support the argument that centrally-mediated mechanisms remain intact in the ageing population. Accordingly, dual-site adaptation data provide compelling new evidence of somatosensation in ageing that will contribute towards the development of an assessment tool to ascertain pre-clinical, age-related changes in the status of cortical function.

Key words: aging; neural plasticity; somatosensory; vibrotactile adaptation.

Introduction

Ageing is characterised by substantial alterations in grey and white matter integrity (Raz et al., 2005), as well as the depletion of neurochemicals and corresponding post-synaptic receptor types (Gao et al., 2013, McQuail et al., 2015). Such declines allude to a reduction in cortical plasticity; yet, the ageing brain possesses a staggering ability to adapt to such losses and preserve performance in a variety of cognitive domains (for a comprehensive review, see Drag and Bieliauskas, 2010). Aspects of somatosensory function may also remain intact across the lifespan, or be restored, despite degradation of skin physiology and concomitant increases in the size of receptive fields (Dinse et al., 2006, Decorps et al., 2014). Although supporting evidence is comparatively sparse, it appears that age-related differences exist in the basic measures of tactile stimulus identification (reaction time [RT] and detection), whereas age-related similarities have been identified in vibrotactile amplitude discrimination (Zhang et al., 2011). This effect emerges with and without single-site adaptation (SSA), which produces a reduction in perceived intensity at one of two stimulus sites and typically leads to degraded performance compared to baseline (for further details, see Hanley et al., 2015). Age-related maintenance of performance, therefore, appears to relate exclusively to the mechanisms underpinning the ability to distinguish between stimuli as opposed to those that govern their identification.

While tactile detection has been established to be dependent on anatomical differences in nerve conduction speed of afferent fibers and receptor morphology at the periphery (Verrillo et al., 2002, Di Iorio et al., 2006), a wealth of literature from animal and human studies suggests that tactile discrimination (with or without adaptation) is mediated by GABAergic (gamma-aminobutyric acid) lateral inhibition within primary somatosensory cortex (S1) (O'Mara et al., 1988, Lee and Whitsel, 1992, Lee et al., 1992, Kelly and Folger, 1999, Whitsel et al., 2000, Tommerdahl et al., 2002, Chen et al., 2003; Whitsel et al., 2003). Those with Autism Spectrum Disorder (ASD) fail to utilise cues from conditioning stimuli and perform similarly during baseline and adaptation trials, due to underlying GABAergic dysfunction (Tannan et al., 2008). Healthy individuals administered with an NMDA (N-methyl-D-aspartate) receptor antagonist (Dextromethorphan, DXM) have also been shown to exhibit a similar attenuation of the typical adaptation response (Folger et al., 2008). Performance on tasks recruiting centrally- as opposed to peripherally- mediated processes is, therefore, likely to decline where central nervous system (CNS) sensitivity is deficient or be

spared where it is thought to be intact. Consequently, whether transient changes in use-dependent plasticity are evident or not appears to reflect the status of CNS function and local competitive interactions between minicolumns (Zhang et al., 2011), suggesting that it is possible to characterise the integrity of cortical processing mechanisms via somatosensory function (Levit-Binnun et al., 2013). This is a particularly important consideration in the context of ageing because early indications of cortical change could assist in the identification of neurodegeneration, prior to the manifestation of observable cognitive deficits.

Determining the precise conditions in which older adults are expected to achieve equivalent performance to young adults is crucial if vibrotactile task performance is to be successfully applied to characterise CNS function. In principle, the identification of intact performance should be applicable to paradigms other than SSA, which engage identical mechanisms. However, whether the maintenance of performance in the ageing population is unique to this type of adaptation is not known. Compared to SSA, dual-site adaptation (DSA) optimises stimulus processing and improves the ability of a participant to discriminate between subtle variations in amplitude (Kohn and Whitsel, 2002, Tannan et al., 2007, Folger et al., 2008, Zhang et al., 2009, Puts et al., 2013). Demonstrating the emergence of improved performance would provide compelling evidence for the maintenance of plasticity and is undoubtedly hugely desirable in the context of age-related change, where decline is expected to be the norm. For this purpose, the present investigation aimed to characterise age-related performance under conditions of DSA, and in doing so, sought to contribute towards research outlining the feasibility of utilising vibrotactile measures to derive inferences on neural plasticity. It was predicted that peripherally-mediated measures of RT would exhibit age-related differences, with older adults demonstrating prolonged and more variable information processing speeds. In contrast, based on the notion that older adults are able to compensate for cortically-mediated changes, it was proposed that they would achieve similar scores with regard to discrimination and improve performance under adaptation conditions to a similar extent as young adults.

Experimental Procedures

Participants: 70 individuals (35 young adults; 35 older adults) were recruited from the general population to take part in the study. Young adult participants were 18-29 years of age

($M=20.60$, $SD=2.35$; 26 female). Older adult participants were 55-70 years of age ($M=61.09$, $SD=4.65$; 23 female). All participants had corrected-to-normal vision and no history of neurological and/or psychiatric conditions. The Mini Mental State Examination (MMSE, Folstein et al., 1975) was used to establish the cognitive health of the older adult participants, all of whom performed within the normal range ($M=29.54$, $SD=0.82$). Participants gave written informed consent prior to taking part in the study. All procedures were carried out with the approval of the local ethics committee (Department of Psychology, Swansea University).

Vibrotactile tasks: Participants completed RT and amplitude discrimination tasks. Sinusoidal, vertical skin displacement stimuli were delivered to the index (D2) and middle (D3) finger of the left hand, via the Brain Gauge (Cortical Metrics; Chapel Hill, NC). The device features two, 5 mm diameter probe tips on which participants lightly rest the corresponding digits. The Brain Gauge is functionally equivalent to the CM4 device (as described by Holden et al., 2012), which has been used to assess information processing in healthy participants and clinical samples (Nelson et al., 2012, Rai et al., 2012).

All vibrotactile pulses were delivered at 25 Hz. The simple reaction time task required participants to respond as quickly as possible to a single 350 μm stimulus, delivered to D2 for 40 ms, with an inter-trial interval of 3000-7000 ms (Figure 1A). During the baseline amplitude discrimination task, participants were asked to determine which of two simultaneously delivered stimuli felt more intense (Figure 1B). Test and standard stimuli were presented for 500 ms. The test stimulus varied between 205–400 μm . In the DSA task, participants were instructed to ignore the first set of vibrations before making the same intensity judgment on the subsequent pair (Figure 1C). The duration of the conditioning stimuli was 500 ms, with an amplitude of 200 μm for both digits (identical to that of the standard stimulus). The conditioning stimuli were followed by an interval before the test phase, lasting 1000 ms. After the test stimuli had been presented, participants had an unrestricted amount of time to make the required intensity discrimination but were instructed to respond as quickly as possible. Both discrimination tasks produced difference limen (DL), regarded as the smallest detectable difference between two stimuli. Lower DLs are indicative of superior performance. Participants responded with their right hand, using the mouse to click on one of two on-screen response options, corresponding to D2 and D3. A 5000 ms inter-trial interval separated each trial. The location of the standard and test stimuli was

randomised across trials. Responses on each 2AFC discrimination task were tracked using a staircase method (identical to that outlined by Hanley et al., 2015).

Procedure: Participants began the testing session by completing the consent form and were subsequently instructed on how to perform the vibrotactile tasks. Older adults also completed the MMSE. They were then seated in front of a computer monitor with the stimulation device positioned on their left-hand side and were presented with training trials to familiarise them with each task. Correct responses on three consecutive trials were required to proceed to the main experimental test. Participants completed a series of 14 simple reaction time trials. The two highest and lowest values were removed to account for the effects of anticipation and inattention, such that the results from 10 trials were analysed. 20 trials of the baseline and adaptation versions of the discrimination task were performed. The order of the tasks was counterbalanced. Test sessions took approximately 20-30 minutes to complete.

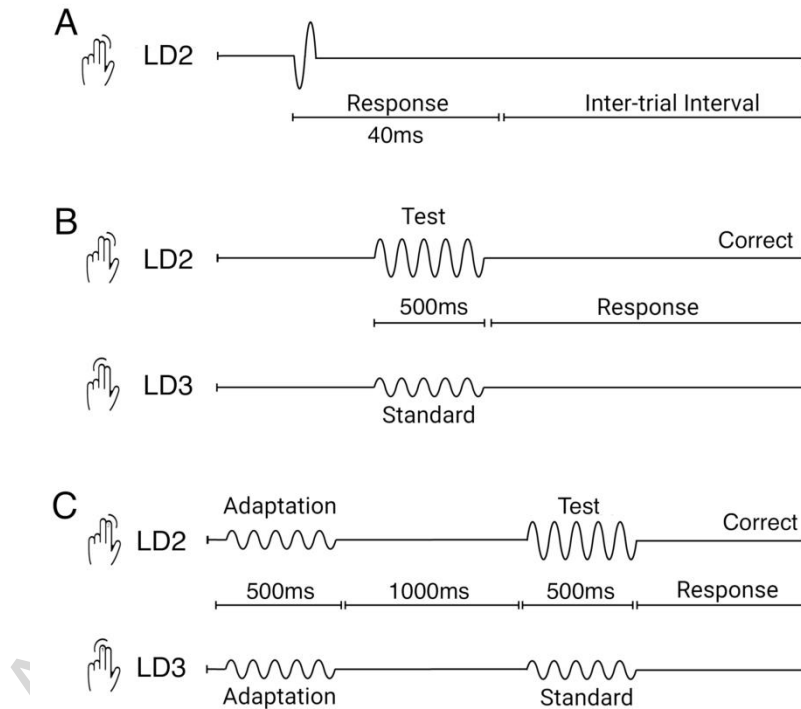


Fig. 1. Schematic representation of the vibrotactile tasks. A) Reaction time: Participants respond as quickly as possible to a single stimulus; B) Amplitude discrimination: Participants determine which of two simultaneously delivered stimuli felt more intense; C) Dual-site adaptation: Participants ignore the first set of vibrations before making the same intensity judgment on the subsequent pair.

Data analysis: Participants with variance exceeding 2 SDs were removed from the sample (four in total) to prevent their scores from skewing the overall distribution of the data. Of the 70 participants tested, 2 were removed from the older adult group due to exceptionally slow RTs, and 2 from the young adult group due to extreme RT variability. This reduced the sample to 33 young adults ($M=20.73$, $SD=2.36$; 24 female) and 33 older adults ($M=61.18$, $SD=4.64$; 22 female). Data from the remaining 66 participants was entered into statistical analysis using SPSS for Windows software (version 22; IBM, New York). Independent and dependent samples t-tests were utilised to test for effects between age groups and performance improvements across the amplitude tasks within each age group, respectively. Pearson's correlation was used to assess the relationship between the tasks and age. All correlations were subject to bootstrapping with 1000 iterations (reported with 95% confidence intervals). Statistical significance was inferred where results were found to be less than, or equal to, the .05 alpha level. Effect sizes were generated and interpreted as outlined by Lakens (2013) (accompanying spreadsheet available via the Open Science Framework: <https://osf.io/wgsi3/?action=view>).

Results

Age-related differences in peripheral and central measures of tactile acuity

A significant difference was found between age groups, with regard to RT ($t(44.926)=-4.534$, $p=.000$, $d=1.116$) and RT variability ($t(54.622)=-2.353$, $p=.022$, $d=.578$), as depicted in Figure 2. In addition, a significant linear relationship was established between age and RT ($r(66)=-.528$, $p=.000$ [.397, .643]), as well as for age and RT variability ($r(66)=.300$, $p=.014$ [.057, .493]), whereby increased age was associated with longer RTs and instability of responses. In comparison, amplitude discrimination did not significantly differ between young and older adults ($t(56.669)=-1.360$, $p=.179$, $d=.336$), and was not found to correlate with age ($r(66)=.159$, $p=.201$ [-.092, .390]).

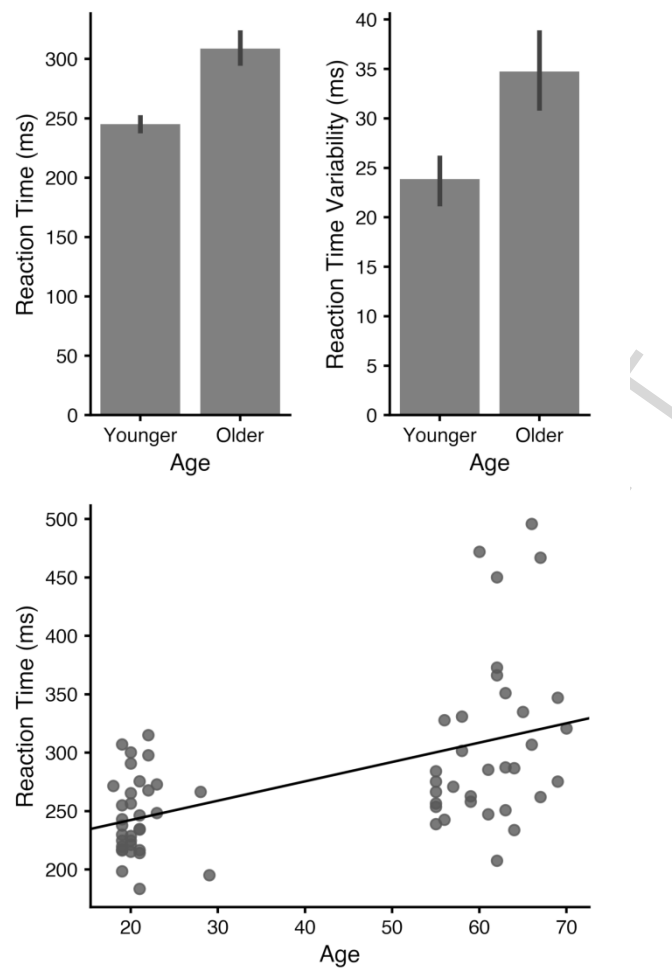


Fig. 2. RT and RT variability differ in accordance with age group. The figure highlights the elevation in RTs exhibited with age, and corresponding variability in responses. Error bars represent ± 1 S.E.M.

The influence of dual-site adaptation in relation to age

Both young ($t(32)=3.912$, $p=.000$, $d=1.385$) and older adults ($t(32)=2.079$, $p=.046$, $d=.735$) achieved significant performance improvements, compared to the baseline discrimination task, under conditions of dual-site adaptation. Furthermore, there was no significant difference in the magnitude of the improvement between age groups ($t(49.770)=.066$, $p=.948$, $d=.016$), as illustrated in Figure 3.

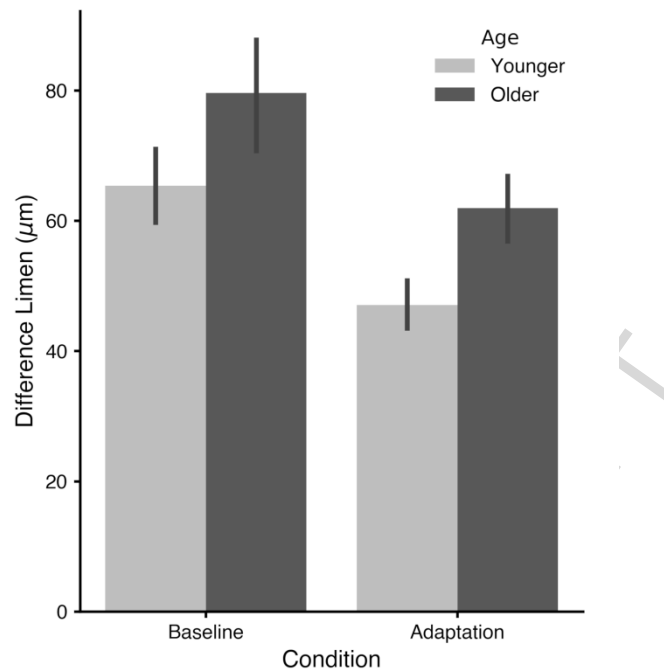


Fig. 3. Magnitude of performance enhancement under dual-site adaptation is comparable between young and older adults. The graph depicts the extent to which dual-site adaptation improved performance thresholds, referred to as difference limen (DL), in each age group. Error bars represent ± 1 S.E.M.

Amplitude discrimination and dual-site adaptation performance were found to be significantly correlated ($r(64)=.441$, $p=.000$ [.259, .608]), inferring that baseline response influences adaptation-based performance. This result did not change while controlling for the effect of age ($r(63)=.420$, $p=.000$ [.225, .602]), as determined by the statistical comparison of correlation coefficients ($p=.884$) (Steiger, 1980).

Discussion

The study aimed to characterise age-related vibrotactile performance, by establishing the influence of ageing on measures of RT and amplitude discrimination. As predicted, older adults exhibited elevated RTs and increased RT variability, while demonstrating equivalent performance to young adults during amplitude discrimination. These results suggest that peripheral and central components of the somatosensory system are differentially affected by the process of ageing. Specifically, aspects of information processing reliant upon S1 response remain intact, while those dependent on nerve conduction speed decline, in the ageing population. To investigate centrally-mediated mechanisms in greater depth, the

amplitude discrimination paradigm was paired with dual-site adaptation stimuli. Under these circumstances, the older group achieved comparable performance enhancements to the younger group. This result represents new insight into the precise conditions in which older adults are expected to sustain performance – evidence which is essential to the future development of somatosensory-driven assessments of CNS sensitivity.

With regard to peripherally-mediated aspects of information processing, such as speed and variability, these have been widely documented to be particularly prone to the effects of ageing across a variety of cognitive domains (Hultsch et al., 2002, MacDonald et al., 2006, Yang et al., 2015), as well as in relation to the somatosensory system (Zhang et al., 2011). Reductions in the efficiency of nerve transmission, in addition to a decline in the structural integrity of the brain, have been proposed to account for this process of slowing across the lifespan (Eckert, 2011). Specifically, up to the age of 70 years, it has been reported that it is primarily losses in white matter, as opposed to grey matter, that underlie age-related change in speed of processing (Hong et al., 2015). Such alterations in neural circuitry likely account for age-related decline in tactile sensitivity, as observed as part of the study.

While the ability of aged participants to quickly and consistently identify the presence of a vibrotactile stimulus declined, the results demonstrate that older adults are able to maintain the capacity to successfully discriminate between supra-threshold stimuli of varying amplitudes. To complement this finding, the introduction of a conditioning stimulus at both digits produced a reduction in DL for both age-groups. Representing the threshold at which an individual can successfully discriminate between two different stimuli, lower DLs are indicative of superior performance. Better discrimination has been associated with the efficiency of GABAergic lateral inhibition (i.e. increased stimulus contrast via reduced spatial extent of receptive fields; Folger et al., 2008, Francisco et al., 2008, Francisco et al., 2011, Nguyen et al., 2013a, Nguyen et al., 2013b), thereby aligning DL to a behavioural marker of plasticity; in this instance, within the somatosensory system.

Accordingly, the facilitation of lower DLs was likely produced by an improvement in gain (described as a sharpening of the response of individual neurons and synchronisation of population level firing; Whitsel et al., 2003), elicited via the identical adaptation stimuli delivered to each digit in the DSA task. In turn, a reduction in perceived intensity at each test site would have been predicted to occur, such that responses to subsequently delivered stimuli with similar characteristics were attenuated, ultimately resulting in the perception of the

novel test stimulus as more distinctive. Older adults were able to discriminate between stimuli with an average just-noticeable-difference of 17 μm less than was possible in the baseline task. This was comparable to the 18 μm improvement demonstrated by the younger group. At a duration of 500 ms, the conditioning stimuli would not have been sufficient to produce adaptation of peripheral nerve fibers (Whitsel et al., 2000, Bensmaia et al., 2005, Leung et al., 2005), providing evidence for the involvement of CNS-mediated plasticity during the execution of the amplitude discrimination tasks (Chiu et al., 2005, Simons et al., 2005, Francisco et al., 2008).

The current findings parallel those of other studies investigating the influence of DSA on amplitude discrimination in young adults (Tannan et al., 2007, Puts et al., 2013), whereas this is the first time that the effect has been noted in an older adult sample. In the context of ageing, where decline is anticipated to be the norm, the emergence of enhanced performance provides compelling evidence for the maintenance of plasticity. Results from the MMSE further allude to the absence of detrimental cortical change in the older adult group by demonstrating a high degree of cognitive functioning. However, inferences into neural plasticity are made on the basis of past literature as the study did not directly measure aspects of brain health. To strengthen the available evidence, further investigations could incorporate MR spectroscopy scans to correlate neurochemical levels with behavioural results (Puts et al., 2011). Additionally, paired-pulse Transcranial Magnetic Stimulation (TMS) paradigms have been shown to provide insight into GABA signalling (Liepert et al., 1997) and could represent the means to determine unique contributions from various receptor types.

To conclude, this study provides initial validation for the use of the DSA metric in assessing the status of cortical function on the basis of somatosensory processing. The results will be valuable to the future optimisation of such inferences on neural plasticity, which could dramatically increase the likelihood of detecting signs of abnormal brain changes at an earlier stage than is typically possible. It is feasible that detection may even occur in advance of observing sub-threshold scores on standardised neuropsychological tests, which have been shown to align with fairly advanced pathology (Villemagne et al., 2013, Vos et al., 2013). Use of the Brain Gauge in this manner would allow for rapid evaluation of somatosensory functioning, from which an individual's scores on a comprehensive battery of tests could be shown to correspond with, or deviate from, a normative sample. Where atypical scores are identified, such individuals could be more closely monitored and referred for further testing

as necessary, allowing maximum time for any subsequent interventions to become effective. Developing the test battery and gathering sufficient data on which to base these normative values represent the next phase of the research.

Acknowledgements

The authors would like to thank Sophie Alderman, Jolie Davies, Chris Osmundsen, and Holly Rees for their assistance with data collection, and Dr Alex Jones (Swansea University) for sharing his programming expertise.

Declaration of interest

MT is co-founder of Cortical Metrics, which licenses distribution of the Brain Gauge from the University of North Carolina. Otherwise, the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

ACCEPTED MANUSCRIPT

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Highlights

- 1.** Age-related differences in somatosensory tasks reflect peripheral, as opposed to central, processing mechanisms.
- 2.** Ageing is associated with slower and more variable information processing speeds in the tactile domain.
- 3.** The ability to discriminate between subtle changes in amplitude remains intact in older adults.
- 4.** Enhanced discrimination ability following dual-site adaptation is maintained in older adults.
- 5.** The study suggests that the status of cortical function could be established on the basis of vibrotactile performance.

ACCEPTED MANUSCRIPT