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Title: The perception of affective touch in Parkinson's disease and its relation to small fibre neuropathy.

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ABSTRACT

Affective touch sensation is conducted by a sub-class of C-fibres in hairy skin known as C-Tactile (CT) afferents. CT afferents respond maximally to gentle skin stroking at velocities between 1-10 cm/sec. Parkinson's disease (PD) is characterised by markedly reduced cutaneous C-fibres. It is not known if affective touch perception is influenced by C fibre density and if affective touch is impaired in PD compared to healthy controls. We predicted that perceived pleasantness to gentle stroking in PD would correlate with C afferent density and that affective touch perception would be impaired in PD compared to healthy controls. Twenty-four PD patients and 27 control subjects rated the pleasantness of brush stroking at an optimum CT stimulation velocity (3cm/sec) and two sub-optimal velocities (0.3cm/sec & 30cm/sec). PD patients underwent quantification of C-fibre density using skin biopsies and corneal confocal microscopy. All participants rated stroking velocity of 3cm/sec as the most pleasant with significantly lower ratings for 0.3cm/sec and 30cm/sec. There was a significant positive correlation between C-fibre density and pleasantness ratings at 3cm/sec and 30cm/sec but not 0.3cm/sec. Mean pleasantness ratings were consistently higher in PD patients compared to control subjects across all three velocities. This study shows that perceived pleasantness to gentle touch correlate significantly with C-fibre density in PD. The higher perceived pleasantness in PD patients compared to controls suggests central sensitisation to peripheral inputs, which may have been enhanced by dopamine therapy.

INTRODUCTION

Cutaneous sensory modalities such as pain and touch are fundamental for normal interaction between organisms, their environment and one another. While the emotional aspect of pain has been acknowledged for a long time (Melzack & Casey, 1968) the affective dimension of touch has only been recognised in recent years (Morrison *et al.*, 2010). Vallbo (1999), using the technique of microneurography, identified and characterised a population of low threshold mechanosensory C- fibres, named C-Tactile afferents (CT). Unlike the more classically described C-fibres, CT afferents did not code for pain or itch, but responded optimally to low force/velocity gentle touch (Vallbo *et al.*, 1999). CT afferents fire maximally when a gentle caressing or “stroking” is applied to the skin. In contrast to myelinated afferents that respond linearly to stimulus velocity, CT afferents respond optimally to a stroking velocity in the range of 1 – 10 cm/sec, which is also rated as the most pleasant. Stimulation velocities below and above this range (1-10cm/sec) produce a sub-optimal CT response determined by lower firing frequency (Loken *et al.*, 2009; Morrison *et al.*, 2010). Furthermore, fMRI studies have demonstrated that stimulation of CT afferents activates areas in the brain that are associated with pleasure, including the insular cortex, as opposed to stimulation of myelinated fibres which activates the somatosensory areas of the cortex (Olausson *et al.*, 2002; Rolls *et al.*, 2003). This emphasises the specialised role of CT afferents in mediating the affective component of the tactile experience. Recent evidence also suggests that there may be a relationship between low threshold CT afferents and pain pathways with CT afferents playing a pain-inhibiting role (Liljencrantz *et al.*, 2013).

The current view of CT afferents is that they provide the neurobiological basis for the formation and maintenance of social bonds and attachment relationships. They are proposed to be integral to an affiliative reward system that also involves several neuropeptides and neurotransmitters including serotonin, dopamine, opioids and oxytocin (Deakin, 1996; Berridge & Robinson, 1998; Le Merrer *et al.*, 2009; Lee *et al.*, 2009; Walker & McGlone, 2013). Moreover, impaired processing of affective touch has been associated with autistic spectrum disorders (McGlone *et al.*, 2007; Cascio *et al.*, 2012; Kaiser *et al.*, 2016). Consequently, it is possible that pathological variations in peripheral nerve structures or central neurotransmitters may cause impaired processing of affective stimuli.

Parkinson's disease (PD) is a neurodegenerative condition characterised by both central monoamine depletion and reduced number of C-afferent fibres (Nolano *et al.*, 2008; Kass-Iliyya *et al.*, 2015). Thus PD presents a good model for investigating the potential effects of central and peripheral neural impairment on affective touch processing. It is not known if affective touch perception is influenced by C-fibre density and if affective touch is impaired in PD compared to healthy controls. PD is also characterised by a range of non-motor symptoms including pain, depression and apathy that may contribute to anhedonia (Aarsland *et al.*, 2009; Defazio *et al.*, 2013a).

In this study, we assessed perceived pleasantness in response to skin stroking in a cohort of PD patients who had their C-fibre afferents quantified by two different methods: skin biopsy and corneal confocal microscopy. We predicted that affective touch perception

would correlate positively with C-fibre afferent density and that pleasantness would be reduced in Parkinson's disease compared to age-matched healthy controls. We also sought to investigate the potential relationship between perceived pleasantness from CT afferent stimulation and other self-reported symptoms such as depression, apathy and pain.

MATERIALS AND METHODS

Participants

Twenty-four PD patients (age 51-78 years, mean age 63.7; 14 males) and 27 healthy volunteers (age 50-71 years, mean age 63.6; 11 males) took part in the study. PD patients were recruited from neurology clinics at Greater Manchester Neuroscience Centre. Nerve conduction studies were performed on all PD participants and none had significant large fibre or demyelinating neuropathy. Assessments were undertaken without withdrawing dopaminergic therapy (the "ON" state). Healthy controls were recruited via the Salford citizen scientist project (<http://www.citizenscientist.org.uk>). Control participants were selected to be free of all significant medical problems, including pain. The study was approved by NRES Committee London - Bromley (Ref No. 15/LO/0252). All participants provided their written informed consent. The conduct of the study adhered to the tenets of the declaration of Helsinki.

Affective touch evaluation

A goat-hair 70 mm wide artist brush was used to deliver strokes by a trained investigator. Experiments were undertaken in a quiet room on an examination couch. Strokes were delivered on each limb across a 10cm section of the skin. The lateral aspects of both

forearms and shins were chosen to deliver brush strokes. One optimum velocity for CT afferents stimulation (3cm/sec) and two sub-optimal velocities (0.3cm/sec and 30cm/sec) were used to deliver brush strokes. For speed accuracy the investigator followed a moving bar across a 10cm on a computer screen, which was not visible to the participant. The purpose-written programme was developed in LabVIEW (National Instruments, Texas, USA); project no. 2013-40, department of medical physics, Salford Royal NHS Foundation Trust. The programme randomised velocities of 0.3 cm/sec, 3 cm/sec and 30 cm/sec. Each velocity was randomised three times producing a total of nine strokes per limb. The programme was designed so the same velocity is not randomised three times in a row to minimise CT afferent adaptation. There was a pause of 10 seconds between consecutive brush strokes to prevent CT afferents fatigue. Study participants rated pleasantness by placing a mark on a 100mm visual analogue scale (VAS) with the descriptor: “neutral/normal” at the lowest end and the descriptor: “very pleasant” at the highest end. The ratings were measured with a ruler and the mean of the three ratings for each velocity was calculated. The overall average rating for each velocity across all four limbs was used for the final analysis.

Small fibre neuropathy

Small nerve fibre quantification was only undertaken in the PD population. Twenty PD patients underwent skin biopsy and corneal confocal microscopy.

Skin biopsies

Two 3-mm punch skin biopsies were taken from the dorsa of both feet. The biopsies were

immediately fixed in 4% paraformaldehyde, cryoprotected in graded solutions of sucrose, frozen and cut on a cryomicrotome (HM450, Microm International, Germany). Six 50 µm sections per biopsy were immuno-stained using rabbit anti-human PGP 9.5 antibody (Abcam, Cambridge, U.K.) diluted 1/200, followed by biotinylated secondary antibody and Avidin D conjugated to horseradish peroxidase (both from Vector Laboratories, Peterborough, UK). The nerve fibres were demonstrated using SG chromogen (Vector Laboratories, Peterborough, U.K.). A pathologist blinded to the participants' clinical details performed tissue analysis. Intraepidermal nerve fibre density, i.e., the number of nerve fibres crossing basement membrane, was quantified according to established criteria and expressed as number per millimetre of epidermal length (Lauria *et al.*, 2010). The mean between right and left intraepidermal nerve fibre density was calculated for each patient and used for analysis.

Corneal Confocal Microscopy

Corneal confocal microscopy is a non-invasive technique that allows *in-vivo* visualisation and quantification of corneal nerves. It is well established as a non-invasive surrogate method for studying small fibre neuropathy correlating significantly with skin biopsies (Quattrini *et al.*, 2007; Chen *et al.*, 2015). Corneal confocal microscopy was performed on both eyes using a Heidelberg Retina Tomograph III with a Rostock Cornea Module (HRT III RCM; Heidelberg Engineering GmbH, Heidelberg, Germany), as previously described (Tavakoli *et al.*, 2013). Four to six high-resolution (1-2 µm) images of the sub-basal plexus of each eye were obtained for all participants. A trained investigator who was blinded to participants' details analysed corneal images separately. Corneal Nerve Fibre

Density: The number of main nerves per square millimetre was quantified and the mean derived from the right and left eye. Corneal nerve fibre quantification was undertaken using semi-automated, purpose-written, proprietary software (CCMetrics; M.A. Dabbah, Imaging Science and Biomedical Engineering, Manchester, UK).

Affective symptoms, apathy and pain

Depression and anxiety:

Affective symptoms were quantified using the Hospital Anxiety and Depression (HADS) Scale (Zigmond & Snaith, 1983). The HADS consists of 14 items, 7 of which relate to anxiety and the other 7 relate to depression. Each item is scored between 0-3. The overall score ranges from 0 to 42 with higher scores representing a greater degree of affective symptoms.

Apathy:

All participants underwent assessment of apathy using the Lille Apathy Rating Scale (LARS) (Sockeel *et al.*, 2006). The LARS consists of 33 items, divided into nine domains. The score ranges from -36 to +36, with higher score representing a greater degree of apathy.

Pain intensity:

Pain was only quantified in PD patients as healthy controls were selected to be pain-free. The Short Form McGill Pain Questionnaire (SFMPQ) (Melzack, 1987) was used for scoring pain intensity. SFMPQ consists of 15 descriptors (11 sensory; 4 affective), which

are rated on an intensity scale from 0-3. SFMPQ also includes a present pain intensity index scored from 0-5 and a visual analogue scale (0-10), which are also included to provide an overall pain intensity score.

Statistical Analysis

IBM SPSS version 22 was used to analyse the data. All data are expressed as mean \pm SEM. Normality of distribution was assessed using histograms and the Shapiro-Wilk test. A repeated measure ANOVA with between subject factor of group (PD vs Controls) and within subject factor of stroking velocity was used. For the purpose of ANOVA a departure from normality of pleasantness ratings at 0.3cm/sec was detected in control subjects therefore a square root transformation of all pleasantness ratings was undertaken to meet the assumption of normality. Individual means relating to demographics and other disease characteristics were compared using the student *t* test and where the data are not normally distributed the Mann-Whitney U test. Correlation between continuous variables was assessed using Pearson's *r* coefficient. A *p* value of less than 0.05 was considered statistically significant. The *p* value was not corrected for multiple comparisons.

RESULTS

Participants' characteristics are summarised in table 1. There was no significant difference in demographics between PD patients and control subjects.

There was a significant positive correlation between perceived pleasantness at 3cm/sec and 30cm/sec and small fibre nerve density measured by both skin biopsies and corneal confocal microscopy in PD patients ($p < 0.05$) (Figure 1).

Pain intensity in PD patients correlated positively with ratings of 0.3 cm/sec (Pearson's $r = 0.483$, $p = 0.02$) but not with pleasantness ratings at other velocities.

No significant relation was found between affective touch ratings and HADS or apathy scores in either PD or control subjects. Apathy and HADS scores were significantly higher in PD compared to controls (Table 1).

For the ANOVA Mauchly's test indicated that the assumption of sphericity had been violated, $\chi^2(2) = 9.41$, $p = 0.009$, therefore multivariate tests are reported ($\epsilon = 0.85$).

Analysis of variance revealed a substantial main effect for velocity with all participants reporting increased pleasantness at 3cm/sec compared to 0.3cm/sec and 30cm/sec (Wilks' Lambda = 0.26, $F_{2,48} = 66.52$, $p < 0.001$, partial eta squared = 0.73). There was also a main effect of group with PD patients rating brush strokes as more pleasant across all three velocities ($F_{1,49} = 5$, $p = 0.030$, partial eta squared = 0.093) but this was most notable at 0.3cm/sec (Figure 2 & Table 1).

DISCUSSION

We have found a linear relationship between C-fibres density in PD patients and perceived pleasantness of gentle brush stroking at 3cm/sec and 30cm/sec however, such relationship was not present with very slow brush strokes (0.3cm/sec) which was also reported as the least pleasant (Figure 2). Pleasantness rating was highest with stroking

velocity of 3cm/sec in both PD patients and healthy volunteers. Similar to previous studies, reported pleasantness was higher at 30cm/sec compared to 0.3cm/sec. (Loken *et al.*, 2009; Macefield *et al.*, 2014) despite both velocities being suboptimal for CT stimulation demonstrated by low firing rate on microneurography (Loken *et al.*, 2009).

We have measured small nerve fibre density in two locations: the hairy skin of the dorsa of both feet and both corneas. Skin denervation in PD is likely to involve CT afferents although corneal denervation is not expected to include CT afferents given their specialist role in affective touch. Nevertheless, corneal confocal microscopy has been shown to provide a surrogate measure of cutaneous C fibres density (Quattrini *et al.*, 2007; Kassiliyya *et al.*, 2015). Therefore the correlation of perceived pleasantness with corneal nerve density is likely to reflect an indirect association.

Although these findings suggest a relationship between small nerve fibre density and perceived pleasantness it is difficult to draw firm conclusions with regards to the role of CT fibres due to correlations being present in a suboptimal stimulation velocity (30cm/sec) and the difficulty in stimulating CT afferents in isolation without stimulating other low threshold mechanoreceptors.

Contrary to our hypothesis, PD patients compared to controls reported higher pleasantness to brush stroking across all velocities despite having significantly reduced C afferents. This was particularly noted at the slow speed (0.3cm/sec), which is the least effective for inducing pleasantness. Interestingly this abnormally high rating of 0.3cm/sec also

correlated with pain intensity in PD, suggesting a potentially common pathophysiology relating to abnormal central sensitisation to reward and pain. This is plausible given the significant overlap between brain regions responsible for processing pain and reward (mesolimbic dopamine pathway, prefrontal medial cortex, insular cortex) as well as the common neurochemistry between the two systems (opioid & dopamine) (Schultz, 2007; Smith & Berridge, 2007; Wager *et al.*, 2007; Leknes & Tracey, 2008). Several studies have provided evidence of upregulation of central processing of nociceptive input, which is postulated to account for the increased prevalence of pain in PD (Defazio *et al.*, 2013b). It is unknown if this also extends to processing of affective touch however this is suggested by the findings of our study.

Another potential explanation for the higher pleasantness rating in our PD patients is that they did not withdraw dopamine therapy during the experiment. Studies have shown that PD patients with impulse control disorders have higher release of dopamine in the ventral striatum during reward related tasks compared to patients who do not exhibit such behaviour (Steeves *et al.*, 2009; O'Sullivan *et al.*, 2011; Wu *et al.*, 2015). Dopamine has also been reported to modulate tactile temporal perception (Nelson *et al.*, 2012). It is possible therefore that dopamine treatment might have influenced the perception of affective touch in our PD cohort. Curiously this poses the question of the potential role of dopamine in coding for affective touch perception.

Although our PD patients had significantly higher scores of apathy and depression compared to controls we did not find a relationship with affective touch ratings at any of

the three velocities. This suggests that variations in affective touch perception may not be an important cause for apathy or mood change and other factors related to PD are more important. However our study confirms higher rates of depression, anxiety and apathy in PD compared to controls, which is widely reported in the literature (Aarsland *et al.*, 2009; Dujardin *et al.*, 2014). This may be secondary to the disease itself or could result from monoamine depletion involving serotonin and noradrenaline as well as dopamine.

CT afferents are an intriguing sub-group of cutaneous small nerve fibres that have only come to light in the last decade. Their function in disease states has not been explored. In this study we have demonstrated a relationship between small nerve fibre density and perceived pleasantness and have documented varying pleasantness across different stroking velocities in a group of patients with Parkinson's disease. Nevertheless, stimulating CT afferents in isolation was not possible without microneurography techniques, which were not available in this study, and we accept this as a limitation. The other limitation is performing the experiment in the "ON" state only. Assessing the affective touch perception in both the "ON" and the practically defined "OFF" states (after withdrawing dopamine) would have been needed to ascertain whether dopaminergic therapy influenced the perceived pleasantness of brush stroking. This question should be addressed in future studies and is of particular relevance given the role of the CT afferents system in social and emotional development.

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Authors Contributions:

All authors agree to be accountable for all aspects of the work.

Lewis Kass-Iliyya: 1) Design of the work; acquisition, analysis and interpretation of data; 2) Drafting the work and revising the manuscript critically for important intellectual content; 3) Final approval of the version to be published.

Matthew Leung: 1) Acquisition of data; 2) Revising the manuscript critically for important intellectual content; 3) Final approval of the version to be published.

Andrew Marshall: 1) Conception and design of the work; 2) Revising the manuscript critically for important intellectual content; 3) Final approval of the version to be published.

Paula Trotter: 1) Design of the work; analysis and interpretation of data; 2) Revising the manuscript critically for important intellectual content; 3) Final approval of the version to be published.

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Francis McGlone: 1) Conception and design of the work; analysis and interpretation of data for the work. 2) Revising the manuscript critically for important intellectual content; 3) Final approval of the version to be published.

Monty A. Silverdale: 1) Conception and design of the work; analysis and interpretation of data for the work; 2) Revising the manuscript critically for important intellectual content; 3) Final approval of the version to be published.

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Abbreviations:

CT: C Tactile

HADS: Hospital and Anxiety Scale

SFMPQ: Short Form McGill Pain Questionnaire

LARS: Lille Apathy Rating Scale

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Table 1. Demographics and clinical characteristics of Parkinson’s disease (PD) patients and healthy controls. Perceived pleasantness to brush stroking marked on a 1-100 visual analogue scale is also provided. Data are presented as Means \pm SEM (range). SFMPQ: Short Form McGill Pain Questionnaire. HADS: Hospital and Anxiety Scale. LARS: Lille Apathy Rating Scale. Means were compared using the student *t* test in all parameters except for pleasantness rating at 0.3cm/sec where the non-parametric Mann Whitney U test was used.

	PD patients (n = 24)	Controls (n = 27)	<i>p</i> value
Gender	14 males, 10 females	11 males, 16 females	0.210
Age (years)	63.7 \pm 1.6 (51 – 78)	63.6 \pm 1.1 (50 – 71)	0.938
Disease duration (years)	7.7 \pm 0.9 years (1.2 – 18)	-	
Hoehn and Yahr Stage.	I = 8, II = 12, III = 4	-	
SFMPQ	23 \pm 2.6 (0 – 51)	-	
HADS	18.9 \pm 1.9 (2 – 34)	8.8 \pm 1.1 (0 – 20)	<0.001
LARS	-20.4 \pm 1.1 (-32 – -9)	-24 \pm 0.8 (-32 – -13)	0.003
Pleasantness at 0.3cm/sec	30.3 \pm 4.3 (5 – 77)	16.8 \pm 2.8 (0 – 58)	0.017
Pleasantness at 3cm/sec	60.3 \pm 4.2 (19 – 92)	55.0 \pm 4.0 (19 – 92)	0.371
Pleasantness at 30cm/sec	48.3 \pm 3.8 (19 – 87)	41.2 \pm 4.6 (1 – 96)	0.247

Figure legends

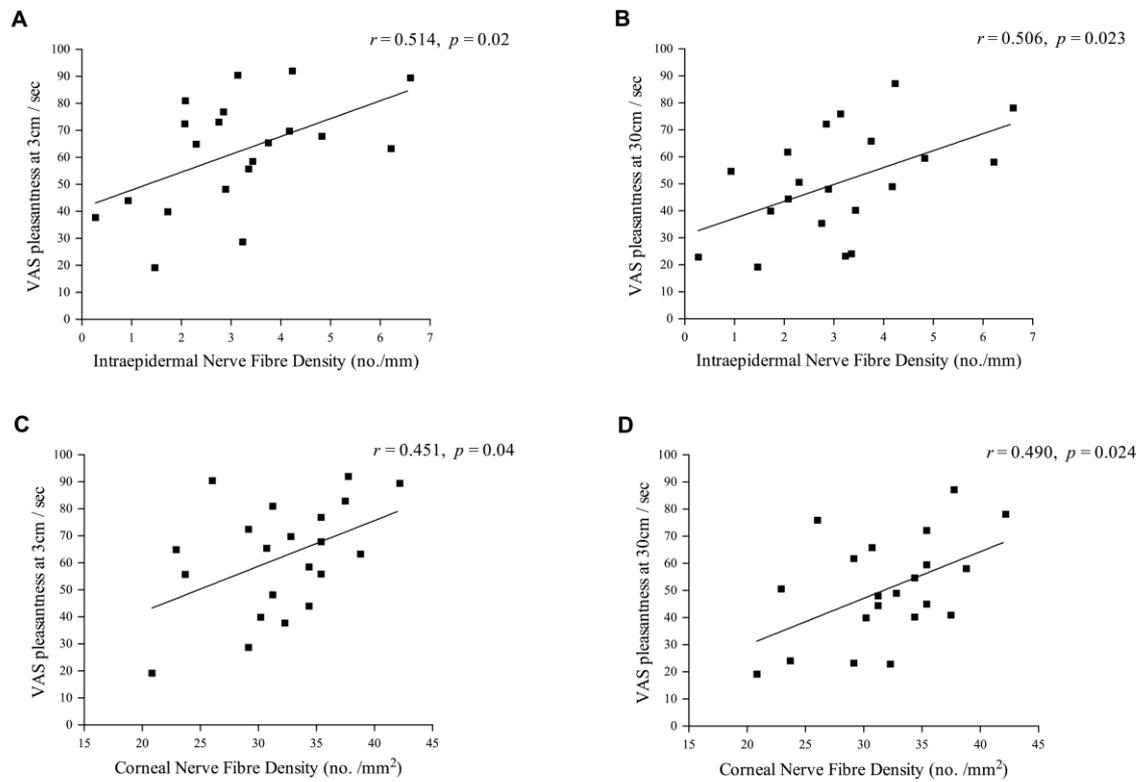


Figure 1 Correlation between pleasantness ratings at 3cm/sec and 30cm/sec and small fibre nerve density measured by skin biopsies (A & B) and corneal confocal microscopy (C & D). Pleasantness rating was measured with a 100mm visual analogue scale (VAS). Correlation coefficient (Pearson's r) and significance are also shown.

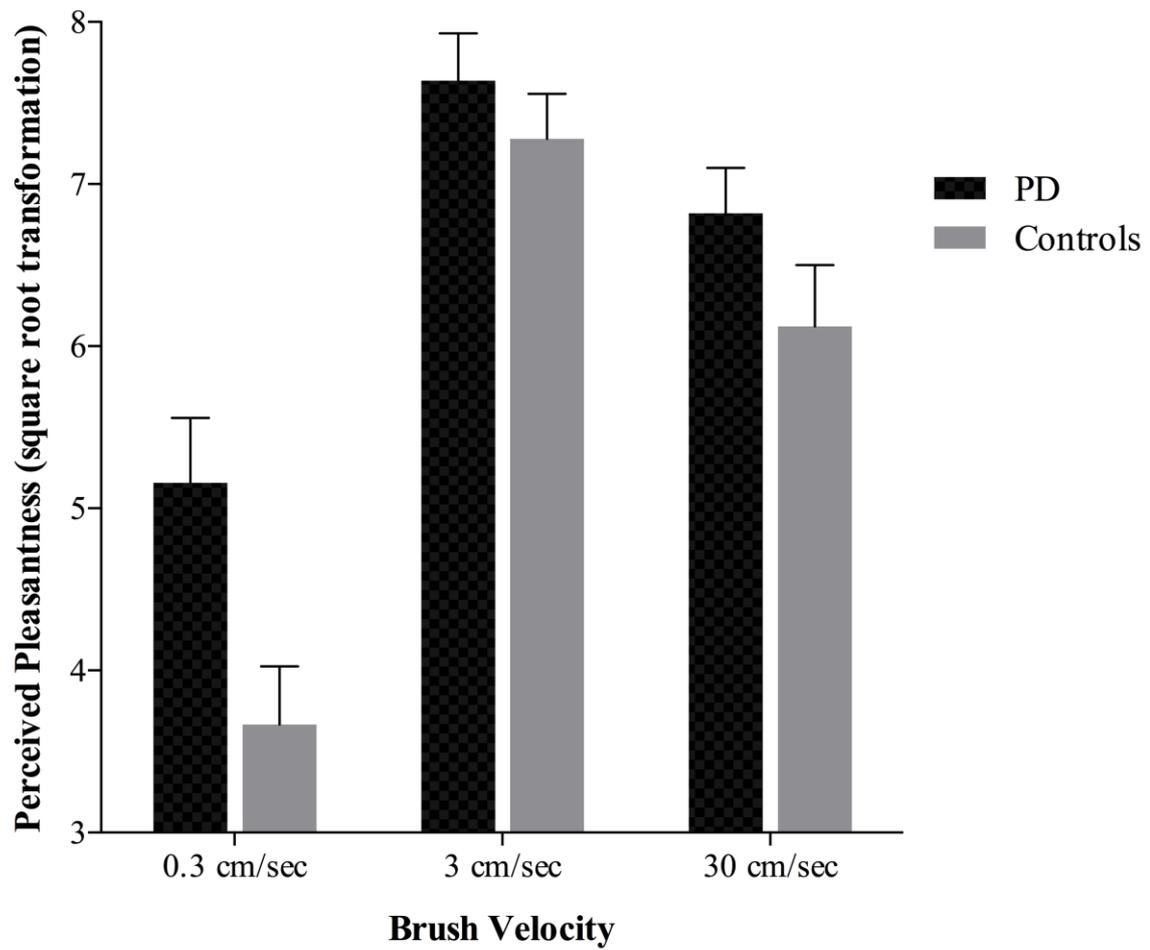


Figure 2 Mean and SEM of affective touch ratings in Parkinson's disease (PD) and Controls using three different velocities of brush strokes. Pleasantness is rated using a 0-100 visual analogue scale (VAS) and square rooted to meet the assumption of normality.