Pain perception and tolerance in patients with frontotemporal dementia

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Introduction

Assessment and management of pain in dementia is problematic for at least three reasons. First, there are difficulties in pain assessment in patients progressively less able to communicate. Second, neurodegenerative changes affect pain processing at different levels. Third, different subtypes of dementia show specific changes along the pain pathways. This issue has only recently started to receive attention, in spite of its physiological and clinical relevance in the aging population [25,26]. For example, lower than average use of analgesics in cognitively impaired patients has been reported [11, 27], and this can be attributed to several factors, such as decreased communication about pain, fewer painful conditions in the demented population, and changes in actual pain experience [30]. A crucial point is thus whether demented patients feel pain in the same way as the cognitively intact elderly.

Among the different subtypes of dementia, Alzheimer Disease (AD) is the one which has been most extensively studied. Many brain areas affected in AD are relevant for pain transmission, e.g. the amygdala, the hypothalamus, the thalamic intralaminar nuclei, the prefrontal regions [17]. These impaired areas are part of the so called “medial system”, which is involved in the affective component of pain [28, 34]. Conversely, the “lateral system”, which is responsible for the discriminative aspects of pain sensation (e.g., the ventroposterior and posterior thalamus projecting to S-I and S-II), is relatively preserved [5]. Consistent with these neuropathological findings, pain threshold has been found to be normal in AD patients [4, 13] but tolerance to experimentally-induced pain is increased, in parallel with cognitive deterioration [4]. However, enhanced fMRI pain-related activity in sensory and affective brain areas has been observed in mild AD [7], and both facial responses to pain [15, 16] and nociceptive motor reflexes [14] have been found to be preserved or even increased in a heterogeneous group of cognitively impaired patients. It is also worth noting that autonomic responses, such as heart and blood pressure responses to pain, are blunted in AD patients [22, 23], all the more so as the disease progresses [3].

Comparatively, less is known on pain processing in other types of dementia. In frontotemporal dementia (FTD) a higher prevalence of loss of pain awareness compared to other dementias was reported by caregivers, possibly indicating deterioration of the medial system [2]. Among FTD patients, those displaying semantic dementia showed more frequently increased responsiveness to sensory stimuli, including pain [33]. So far, no experimental pain studies have been conducted in these patients. On the basis of these considerations, in the present study we measured pain threshold and tolerance in clinically diagnosed FTD patients showing Single Photon Emission Computerized Tomography (SPECT) cerebral hypoperfusion.

Materials and methods

Patients

Thirty-two consecutive patients diagnosed with FTD according to the criteria of Neary et al. (1998) were recruited from the Dementia Center of the University of Turin and the S. Lazzaro Medical Center of Alba. The core diagnostic features suggested were: insidious onset and gradual progression, early decline in social interpersonal conduct, impairment in regulation of personal conduct, emotional blunting, loss of insight. Supportive diagnostic features were behavioral disorder, speech and language alteration, and physical signs [19]. They subsequently underwent structural (magnetic resonance imaging, MRI) and functional (single photon emission computed tomography, SPECT) imaging, and only those with a positive SPECT report (hypoperfusion including frontal and/or temporal lobes) were included in the study. Nine patients were excluded because their SPECT was not available (N=2) or negative (N=7).

The final 23 patients (12 males and 11 females, mean age 66.1 ± 8.2 years, mean education 5.8 ± 4.2 years) , communicative and collaborative, underwent neuropsychological assessment including the Mini Mental State Examination (MMSE) [12] and the Frontal Assessment Battery (FAB) [1, 8, 32]. Eleven patients were treated with antidepressant drugs (venlafaxine, N=1; paroxetine, N=4; amitryptiline, N=1; sertraline, N=1), 4 patients received anticholinergic treatment

(donepezil, N=3; rivastigmine, N=1), 4 patients were administered antipsychotic drugs (olanzapine, N=3; haloperidol N=1), 1 patient was treated with antihypertensive drugs (atenolol), and 3 patients with antidiskynetic drugs (levodopa/benserazide). They were subdivided according to two different criteria: 1) *Neuropsychological criterion*: patients were sorted out according to their score on the FAB test. The FAB is a cognitive and behavioural battery for executive functions examination with six subtests: abstract reasoning (e.g. similarities), mental flexibility (e.g. phonological verbal fluency), motor programming (e.g. Luria's motor series), interference (e.g. conflicting instructions), inhibitory control (e.g. go-no go task), and environmental autonomy (e.g. social contact and dependence) [8]. We chose the FAB test because it is both easy to administer at bedside and reliable in assessing frontal lobe function, differentiating FTD from other types of dementias [32]. Eighteen patients obtained a pathological FAB score below cut-off value (<13.5) [1, 8], and are hereafter referred to as the "*FAB Group*" while four patients scored normal. 2) *Neuroradiological criterion*: thirteen patients were selected, who showed strictly localized frontal and/or temporal SPECT cerebral hypoperfusion (Fronto-Temporal, "*FT Group*", see Fig 1). In twenty patients hypoperfusion was bilateral, in three it was limited to the left side. Hypoperfusion evaluation was qualitative, based on the radiologist report, and we did not attempt further quantification.

Eighteen healthy subjects (11 males and 7 females; mean age 63.3 ± 6.4 years) were recruited among relatives of the University staff and used as controls. Their history was taken, in order to exclude pathological conditions and cognitive impairment. No significant difference was found between FTD patients and controls for demographic factors (Table I).

Two female examiners (a psychologist and a medical doctor) carried out the psychophysical measurements, which were an extension of the normal neurophysiological assessment. All patients were nonetheless informed about the aim and procedures of the study (assessment of pain threshold and tolerance in FTD patients) and written informed consent was obtained from the subject and/or a collateral source. All the procedures were performed following the rules approved by our

Institutional Review Board (IRB) for the assessment of sensory thresholds and quantitative sensory testing (QST) in demented patients.

Pain stimuli

Electrical stimuli (200 μs monophasic square pulses of constant current, in the range 2–50 mA) were delivered in ascending sequence, with steps of 2 mA, on the back of the hand by means of a computer-controlled somatosensory stimulator (Galileo Mizar NT, EB Neuro, Florence, Italy). The step size was set at 2 mA for all subjects, in order to reduce the psychophysical assessment duration, especially in the patient population. The interval between stimuli was variable in a range of 7-15 s. The subjects were asked whether they detected the stimulus (tactile threshold), and, when they did, whether it was painful (pain threshold) and whether the pain sensation was unbearable (pain tolerance). The stimulus sequence was applied on both hands in random order, and for each subject six variables were obtained: right-hand and left-hand tactile threshold, pain threshold and pain tolerance. Tactile threshold was defined as the smallest intensity able to produce a tactile sensation, pain threshold as the smallest intensity able to produce pain, and pain tolerance as the smallest intensity able to induce an unbearably painful sensation. Care was taken to ensure that the subjects understood the questions. All patients were communicative, with mean MMSE = 21.7 ± 6.1 points. If the subject did not report an unbearable painful sensation by the end of the sequence, the assessment was stopped at 50 mA, as this represents quite a strong stimulus. In such case, tolerance was computed as being 50 mA (see Table II for frequency of subjects with pain threshold and tolerance above 50 mA).

Statistical analysis

Statistical analysis was carried out by means of three-way mixed ANOVA for repeated measures, followed by the *post hoc* Student-Newman-Keuls test (SNK) for multiple comparisons. We considered group (patients, controls) as the independent factor, and condition (tactile threshold,

pain threshold, pain tolerance) and side (right, left) as repeated within-subject variables. Effect sizes (Cohen's *d*) were then calculated [6]. Chi-square analysis was computed on frequency distributions of tactile and pain thresholds and pain tolerance above each variable global (across group and side) average. Moreover Chi-square analysis was calculated on frequency distributions of pain threshold and tolerance above 50 mA. Yates correction was applied. Data are presented as mean ± SD and the level of significance was set at $P < 0.05$. The analysis was performed with Statistica, version 9 for Windows.

Results

We carried out three different comparisons, as follows: 1) *global analysis*: the entire sample of patients (n = 23) vs. controls (n = 18); 2) *neuropsychological analysis*: the FAB group (n = 18) vs. controls; 3) *neuroradiological analysis*: the FT group (n = 13) vs. controls (see Methods). No differences were found among the groups for age or MMSE score. Demographic and cognitive features of all groups are presented in Table I.

Global analysis

In the control group the tactile threshold was 3.9 ± 1.1 mA for the right hand and 3.8 ± 0.9 mA for the left hand, whereas in the patient group it was 5.1 ± 2.0 mA for the right hand and 5.2 ± 2.5 mA for the left hand. As to the pain threshold, the right and left pain thresholds were 14.9 ± 4.6 mA and 14.8 ± 6.1 mA respectively in the control group, and 25.4 ± 15.8 mA (right) and 24.6 ± 15.8 mA (left) in the patient group. Pain tolerance was 28.9 ± 10.3 mA (right) and 27.3 ± 11.4 mA (left) in the control group, and 36.0 ± 16.1 mA (right) and 35.6 ± 15.8 mA (left) in the patient group. Data are summarized in Fig 2. Global averages across group and side were 4.6±1.6 for tactile threshold, 20.5±13.0 for pain threshold and 32.4±14.2 for pain tolerance. These global averages were used as critical values for Chi-square computation. A significant difference between groups for tactile [$\chi^2(1)=6.4$, $P<0.02$] and pain threshold [$\chi^2(1)=8.1$, $P<0.005$] was obtained, whereas no difference was observed in pain tolerance. The Chi-square analysis on frequencies of pain threshold

and tolerance above 50 mA was also computed. The results showed a significant difference between groups for pain tolerance [$\chi^2(1)=4.7$, $P<0.04$], whereas no difference was observed in pain threshold.

The three-way ANOVA showed significant differences between groups [$F(1,39) = 6.3$, $P < 0.02$] and conditions [$F(2,78) = 106.8$, $P < 0.001$], whereas no differences were found for side and interaction effects. Multiple comparisons with the *post-hoc* SNK test showed significant differences between groups for pain thresholds (right: $P < 0.02$, left: $P < 0.03$), but not for tactile threshold or pain tolerance. As expected, within group comparisons showed significant differences between all conditions ($p < 0.001$). Interestingly, no differences were found between controls pain tolerance and patients pain threshold.

The Cohen's *d* value, as measure of the effect size, was computed and a large effect was obtained for tactile threshold (right: d=0.8, left: d=0.8) and pain threshold (right: *d*=0.9, left: *d*=0.8), whereas only a medium effect was observed for pain tolerance (right: *d*=0.5, left: *d*=0.6).

Neuropsychological analysis

The mean FAB score for the FAB Group, corrected for age and education, was 10.0 ± 2.5 points. The tactile threshold was 5.2 ± 2.2 mA for the right hand and 5.3 ± 2.7 mA for the left hand. As to the pain threshold, it was 25.9 ± 17.4 mA (right) and 25.2 ± 16.9 mA (left). Pain tolerance in the FAB group was 35.9 ± 16.9 mA (right) and 35.7 ± 16.3 mA (left). Data are summarized in Fig 3. Global averages across group and side were 4.6±1.6 for tactile threshold, 20.2±13.4 for pain threshold and 31.9±14.2 for pain tolerance. These global averages were used as critical values for Chi-square computation. Compared with the global analysis, similar results were obtained with a significant difference between groups for tactile [$\chi^2(1)=5.7$, $P<0.02$] and pain threshold [$\chi^2(1)=8.1$, $P<0.04$] and no difference for pain tolerance. The Chi-square analysis on frequencies of pain threshold and tolerance above 50 mA was also computed. As in the global analysis, a significant

difference was observed between groups for pain tolerance [$\chi^2(1)=6.1$, $P<0.02$], whereas no difference was observed in pain threshold.

As for the global analysis, the three-way ANOVA again showed significant differences between groups [$F(1,34) = 5.8$, $P < 0.03$] and conditions [$F(2,68) = 91.9$, $P < 0.001$], whereas no differences were found for side and interaction effects. Multiple comparisons with the *post-hoc* SNK test showed significant differences between groups for pain thresholds (right: $P < 0.03$, left: $P < 0.04$), but not for tactile threshold or pain tolerance. Within group comparisons showed significant differences between all conditions ($p < 0.001$). Again, no differences were found between controls pain tolerance and patients pain threshold.

The Cohen's *d* value was computed and again a large effect size was obtained for tactile threshold (right: d=0.8, left: d=0.8) and pain threshold (right: *d*=0.9, left: *d*=0.8), whereas only a medium effect was observed for pain tolerance (right: *d*=0.5, left: *d*=0.6).

Neuroradiological analysis

In the FT group tactile threshold was 5.2 ± 2.4 mA for the right hand and 5.1 ± 1.5 mA for the left hand. Right and left pain thresholds were 28.0 ± 16.9 mA and 26.3 ± 17.3 mA, respectively. Pain tolerance was 41.1 ± 14.5 mA (right) and 39.8 ± 14.9 mA (left). Data are summarized in Fig 4. Global averages across group and side were 4.4±1.4 for tactile threshold, 20.0±12.9 for pain threshold and 33.3±13.7 for pain tolerance. These global averages were used as critical values for Chi-square computation. A significant difference between groups was observed for tactile [$\chi^2(1)=4.8$, $P<0.03$] and pain threshold [$\chi^2(1)=4.8$, $P<0.03$], and also for pain tolerance [$\chi^2(1)=5.5$, $P<0.02$].

As for the global and neuropsychological analysis, the Chi-square on frequencies of pain threshold and tolerance above 50 mA was computed. The analysis again showed a significant difference between groups for pain tolerance [$\chi^2(1)=6.6$, $P<0.01$], whereas no difference was observed in pain threshold.

The three-way ANOVA showed significant differences between groups [$F(1.29) = 10.8$, $P < 0.003$], conditions [$F(2,58) = 102.61$, $P < 0.001$] and condition * group [$F(2,1) = 4.7$, $P < 0.02$], whereas no differences were found for side and other interaction effects. Multiple comparison with the *post-hoc* SNK test showed significant differences between groups not only for pain thresholds (right: $P < 0.01$, left: $P < 0.02$), but also for pain tolerance (right: $P < 0.01$, left: $P < 0.02$). Again, differences for tactile thresholds were not significant. Within group comparisons showed significant differences between all conditions ($p < 0.001$). Once more, no differences were found between controls pain tolerance and patients pain threshold.

Contrary to the previous analysis, the Cohen's *d* value showed a large effect size for all thresholds: tactile threshold (right: d=0.7; left: d=1.0), pain threshold (right: d=1.1, left: d=0.9) and pain tolerance (right: d=1.0, left: d=0.9).

Discussion

This is the first experimental study on pain in FTD patients. It examines three psychophysical measures, namely tactile threshold, pain threshold and pain tolerance, in patients whose selection is based on a) clinical diagnosis of frontotemporal dementia, and b) cerebral hypoperfusion in frontotemporal lobes, as assessed by means of neuroimaging (SPECT). The main findings can be summarized as follows: 1) pain threshold is increased; 2) pain tolerance is increased with respect to age-matched healthy controls; 3) as far as tactile thresholds are concerned, our analysis with ANOVA produced no significant differences between patients and controls. However, the Chi-square analysis evidenced an higher number of patients with increased tactile threshold and the computation of effect sizes showed that tactile thresholds were as big as for pain threshold and tolerance, which caution us from drawing definitive conclusions. These ambivalent results suggest that there might be only a small tendency of more affection of pain-related thresholds compared to somatosensory thresholds.

Some important considerations have to be made. In fact, the analysis was performed on our global patient sample, as well as on two different (and overlapping) subsets of patients, the first selected on the basis of the FAB score, the second on the basis of exclusive localization of cerebral hypoperfusion in the frontal and/or temporal lobes. In the global sample, which included some patients with normal FAB score and some patients with a more generalized hypoperfusion pattern extending to parietal lobes, we found abnormally high pain thresholds, but normal pain tolerance and tactile thresholds. These findings were exactly replicated in the patients selected by the FAB score (FAB group). Conversely, in the patients selected by frontotemporal hypoperfusion (FT group), pain tolerance was also increased, in addition to pain thresholds. Noteworthy, in all samples patient pain thresholds increase was quite large, as much as to overlap control pain tolerance values.

It has been suggested that pain threshold is a sensory-discriminative aspect of pain sensation, which is mediated by the lateral pain system, while pain tolerance represents an affective aspect that is mediated by the medial pain system [4, 26]. Therefore, it can be hypothesized that the strict neuroradiological criterion evidencing pain tolerance increase, might better reflect neuroanatomical changes, and better select patients with compromised medial pain system areas, such as the anterior cingulate cortex (ACC),the insula, and the prefrontal cortex [21], all of which show atrophy in FTD [24]. Also noteworthy is the fact that by stopping our stimulation sequence at 50 mA, we introduced a saturation effect, which may have caused an underestimation of tolerance increase (see below).

It is also clear from our study that the observed changes in pain processing very much depend on how the diagnosis of FTD is performed. The clinical diagnosis alone, mainly based on neuropsychological testing, may fail to isolate the specific frontal and temporal impairment. Conversely, neuroimaging techniques, such as SPECT, may reveal specific frontal and temporal anatomical changes that are more specifically related to some aspects of pain processing. In this regard, our study emphasizes the need to identify specific subtypes of dementia and related brain lesions when assessing pain perception in patients with impaired cognition, a concept that has been

stressed many times in the past few years [25, 26]. Therefore, whether or not thresholds and tolerance are affected may depend on the criteria that have been adopted for diagnosis.

Our findings differ in part from those described in AD. In fact, while a selective loss of the affective component of pain has been reported in AD patients [4] with conserved aspects of the sensory-discriminative component [13], here we constantly found also elevated pain thresholds. These results are also markedly at variance with the increase in pain experience suggested for vascular dementia (VaD). Although no experimental studies employing psychophysical measures have been conducted, "possible" VaD patients reported pain of a significantly higher intensity than non-demented elderly people [29], with analgesics use being almost three times that of AD patients [31]. This opposite pain pattern has been attributed to deafferentation, caused by subcortical white matter lesions [9, 18].

Clinical studies on pain in FTD patients are only occasional. In one such study, the authors compared a wide array of behavioural changes in AD, VaD and FTD patients. Loss of pain awareness was included among the behavioural disturbances best able to discriminate FTD from other patients [2]. This is in agreement with our results, although the indirect method used (a semi-structured questionnaire administered to caregivers) limits the comparison. Also in another study, comparing semantic dementia (a variant of FTD), with the apathetic (FTD-A) and disinhibited (FTD-D) forms of FTD, loss of pain awareness was quite frequent, with a peak of 45% in FTD-A [33]. In addition, for more than half the semantic dementia patients an exaggerated response to pain and other sensory stimuli was also reported, but unfortunately, here again the evidence was only indirect. In our study, although not differentiating among FTD subtypes, we did never find a decrease in pain threshold or tolerance. The experimental setting is however quite different from the clinical situation, where pain affect evoked by chronic pain has certainly a much more complex impact on the pain experience.

There are some limitations of the present study that need to be discussed. First, the number of participating subjects is relatively small, due to the low prevalence of the disease and we cannot

completely rule out a possible CNS pharmacological effect in patients under therapy. Second, psychophysical measures are subjective verbal reports. To be reliable, they must therefore be assessed in communicative patients. At least in the initial and intermediate stages of dementing illnesses, clinical pain assessment seems to be as reliable as in cognitively unimpaired elderly [10, 20]. Thus, we selected patients with only a mild to moderate degree of cognitive impairment, as assessed by MMSE. This limits the generalization of our findings. One way to circumvent the need for communication when assessing pain sensitivity is to measure autonomic responses. While no data are available specifically for FTD, in AD, heart responses to pain expectation and pain stimulation [22, 23] as well as blood pressure changes [23] and sympathetic skin responses [14] are blunted. Moreover, the decline in autonomic responsiveness correlates with the degree of cognitive impairment, as shown by the slowing of EEG activity [3]. In future research, it would be interesting to know whether FTD patients exhibit the same changes. Third, we limited the electrical stimulation to a maximum of 50 mA for ethical constraints, and this may have led to a saturation effect due to an artificial reduction of the variance in pain threshold and tolerance. Nevertheless, the Chi-square analysis showed that the frequencies of subjects with a pain tolerance above 50 mA is higher in the patient population. These data suggest that the increase in pain tolerance observed in the patients group may be an underestimation of the increase that we would have observed without limiting the stimulation. Fourth, the step-size of 2 mA may not allow for sufficiently fine-grained analysis, preventing the detection of very small differences in tactile thresholds. Fifth, the inherent biases generated by using multiple testing in a study of this kind must be recognized.

In conclusion, this study adds on our knowledge of pain in dementias, highlighting the modifications of pain threshold and pain tolerance in patients displaying frontotemporal hypoperfusion. However, no definite conclusions can be drawn about tactile impairment. It also emphasizes the importance of a correct diagnosis when assessing pain in the demented patient, for the diagnostic criteria may make a big difference when measuring pain threshold and tolerance.

Future studies should focus on different subtypes of dementias, examining their impact on the different pain components while correlating with precise neuropathology.

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Conflicts of interest

We declare that we have no conflicts of interest.

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Figure legends

Fig. 1 - SPECT from two representative patients, one showing hypoperfusion in the frontal lobes (left), the other in the frontal and anterior temporal lobes (right).

Fig. 2. Global analysis. Tactile threshold, pain threshold and pain tolerance in response to electrical stimulation of both hands in patients (gray columns) and in age-matched control volunteers (white columns). Differences are significant only for pain threshold.

Figure 3. Neuropsychological analysis. Tactile threshold, pain threshold and pain tolerance in response to electrical stimulation of both hands in the "FAB group" of patients (gray columns) and in age-matched control volunteers (white columns). Differences are significant only for pain threshold.

Figure 4. Neuroradiological analysis. Tactile threshold, pain threshold and pain tolerance in response to electrical stimulation of both hands in the "SPECT group" of patients (gray columns) and in age-matched control volunteers (white columns). Differences are significant for both pain threshold and tolerance.

Table I – *Patients characteristics*

Groups	**N (male/female)**	**Age (years)**	**Education (years)**	**MMSE**	**FAB**
Controls	18 (11/7)	63.3 ± 6.4	NA	NA	NA
All patients	23 (12/11)	66.1 ± 8.2	5.8 ± 4.2	21.7 ± 6.1	11.2 ± 3.5
FAB group (subgroup of "All patients")	18 (9/9)	66.3 ± 7.3	6.5 ± 4.3	20.9 ± 6.6	9.9 ± 2.5
FT group (subgroup of "All patients")	13 (7/6)	67.8 ± 7.5	5.9 ± 4.9	21.6 ± 6.6	11.3 ± 3.7

MMSE = Mini Mental State Examination.

FAB = Frontal Assessment Battery

FT = Fronto-temporal

NA = Not Available

Table II – *Frequencies of subjects with pain threshold and tolerance above 50 mA*

	Patients			**Controls**
	All patients [n(%)]	*FAB subgroup [n(%)]*	*SPECT subgroup [n(%)]*	
Pain Threshold >50 mA	3 (13%)	3 (16.6%)	2 (15.4%)	0 (0%)
Pain Tolerance > 50 mA	11 (47.8%)	10 (55.5%)	8 (61.5%)	2 (11%)

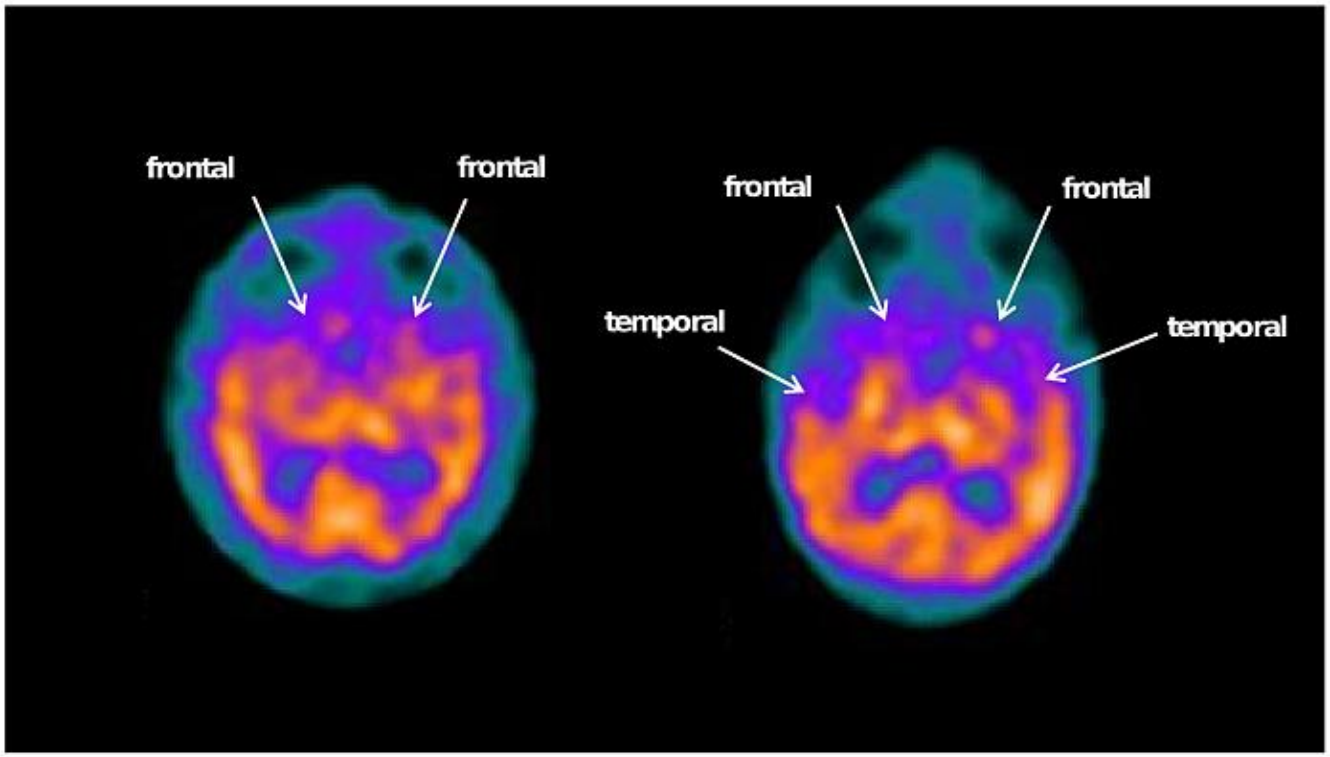

FIG. 1

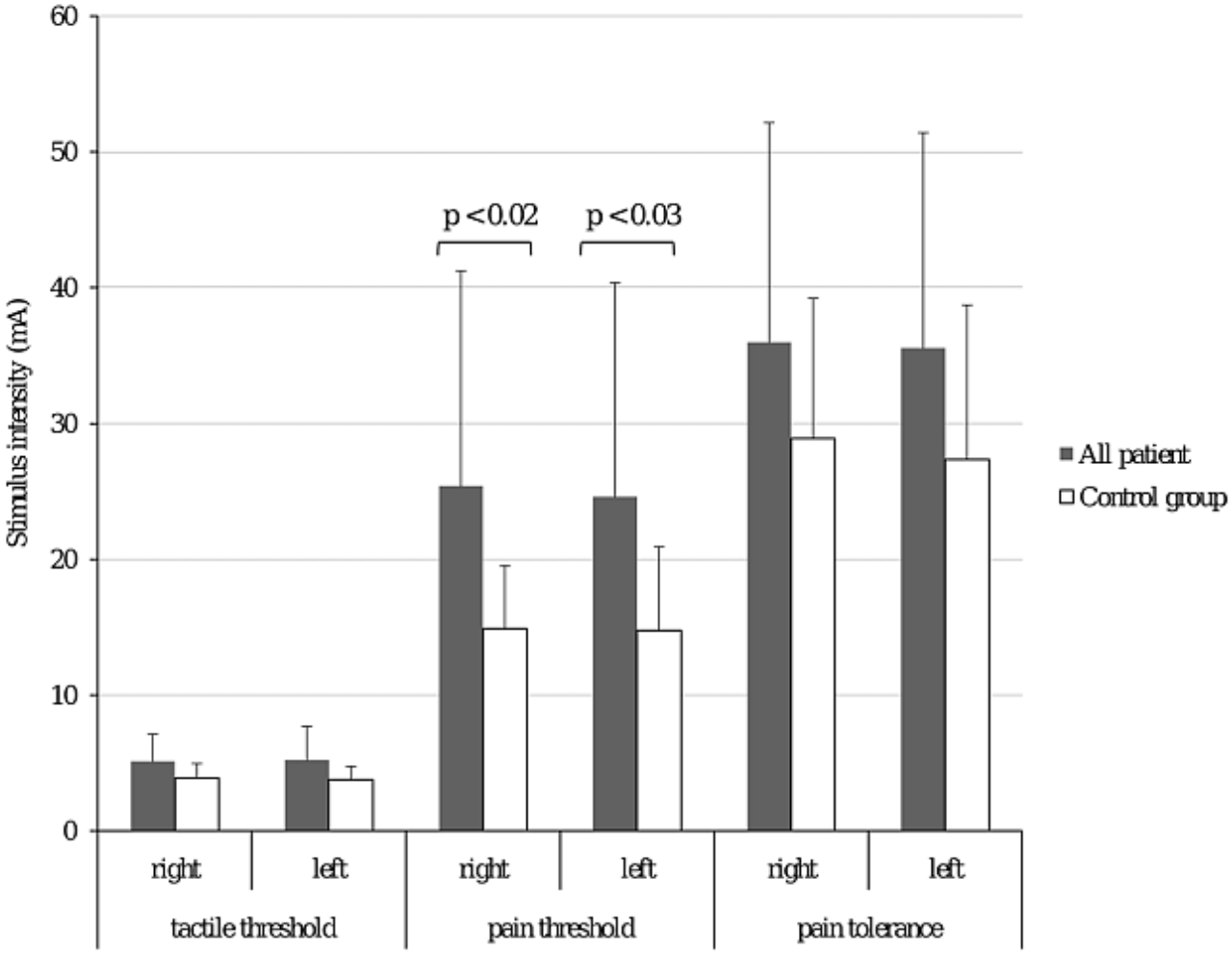
60
50
40
30
20
10
0
Stimulus intensity (mA)
p <0.02
p <0.03
All patient
Control group
right
left
right
left
right
left
tactile threshold
pain threshold
pain tolerance

FIG. 2

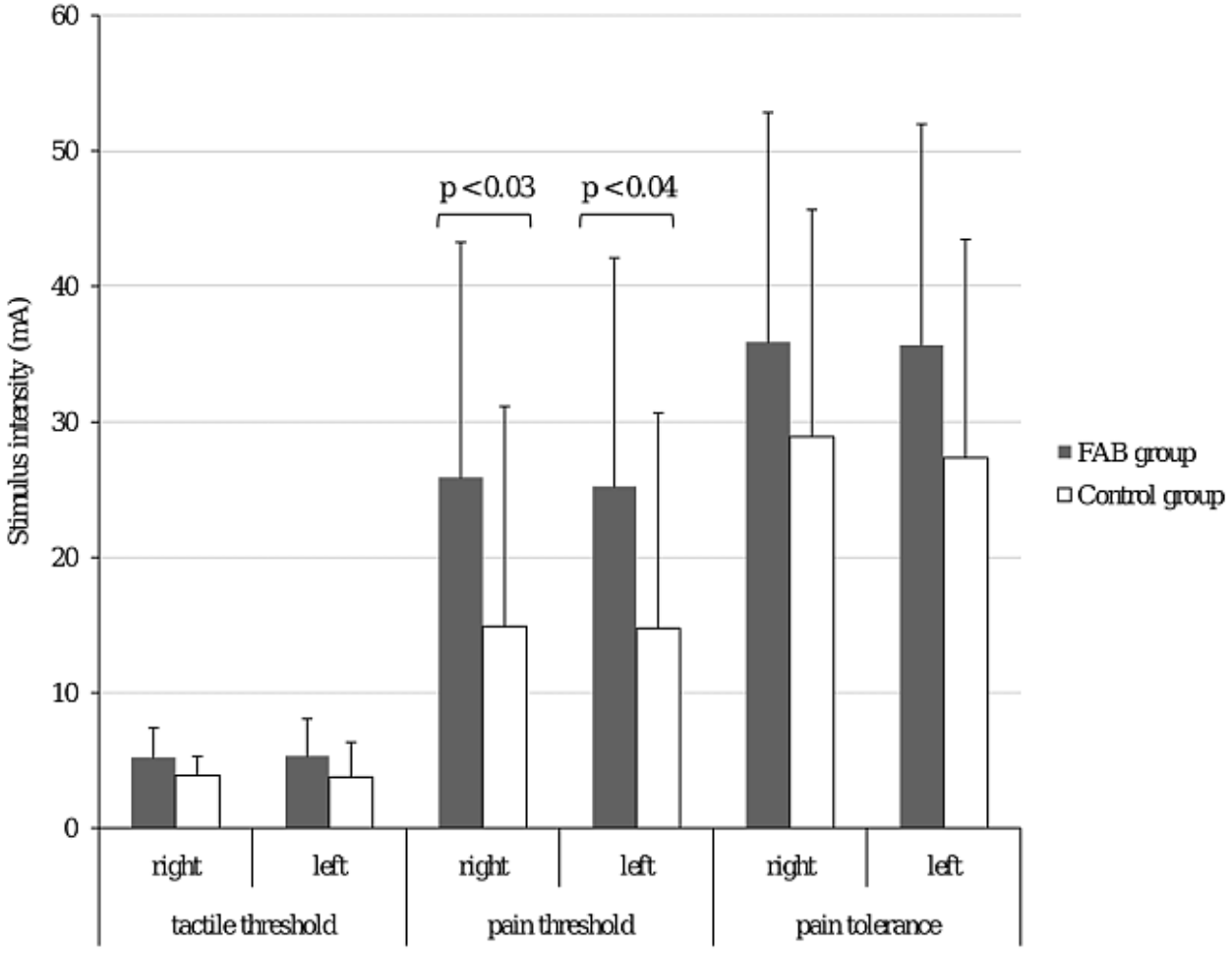
60
50
40
30
20
10
0
Stimulus intensity (mA)
p < 0.03
p < 0.04
right
left
right
left
right
left
tactile threshold
pain threshold
pain tolerance
FAB group
Control group

FIG. 3

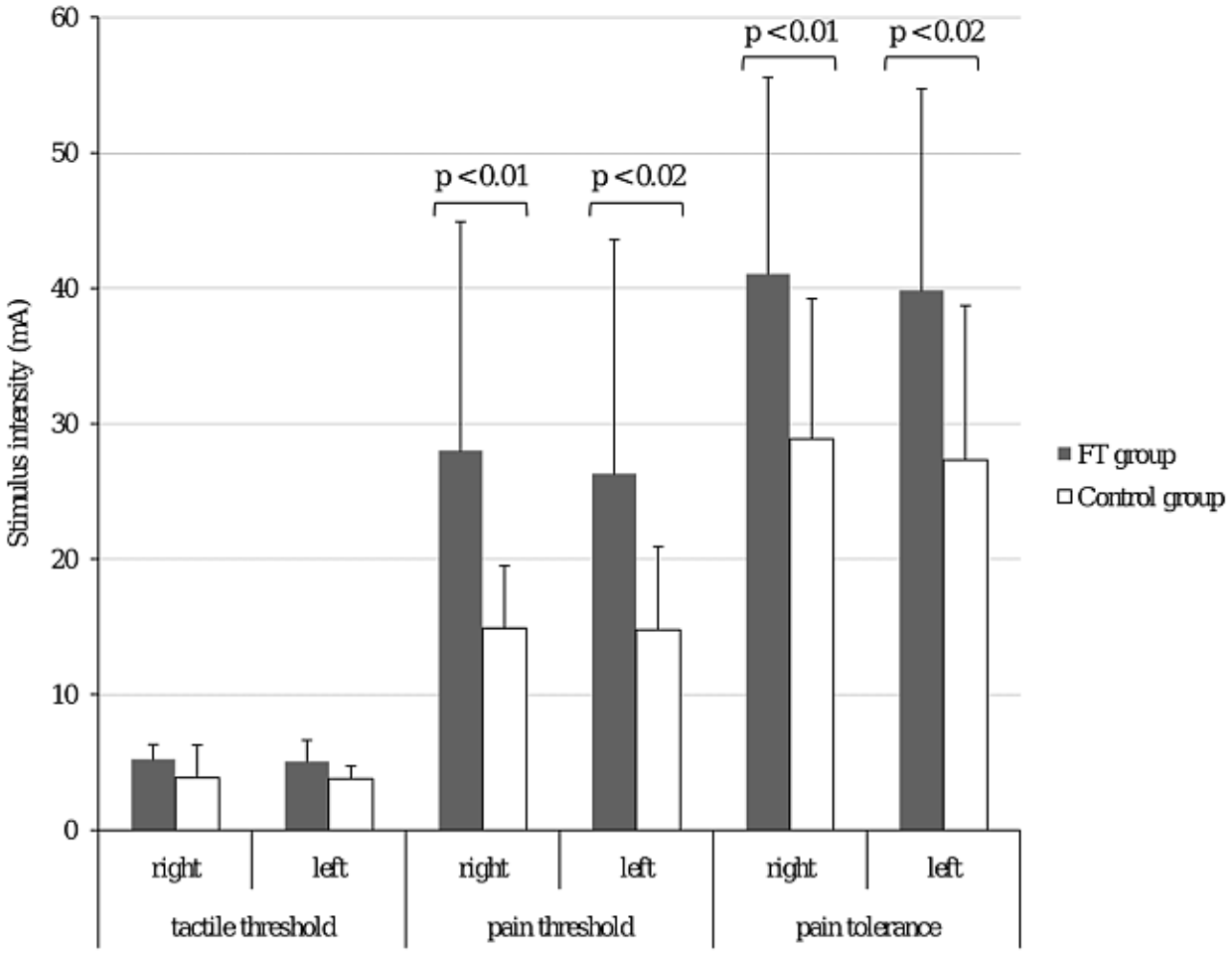
60
50
40
30
20
10
0
Stimulus intensity (mA)
p < 0.01
p < 0.02
p < 0.01
p < 0.02
right
left
right
left
right
left
tactile threshold
pain threshold
pain tolerance
FT group
Control group

FIG. 4