The association between inhibition and pain tolerance in the elderly: Evidence from event-related potentials

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Abstract

Background: Age-related alterations in both pain perception and inhibitory functions have been observed, but the relationship between the two in older adults remains unclear. Previous studies were mainly based on behavioural measures which do not allow assessment of underlying neural mechanisms.

Methods: The present study evaluated the association between inhibition and pain perception in 26 healthy elderly volunteers. Cognitive inhibition was assessed by Stroop interference tests and response inhibition by a Go/No-go task. Event-related potentials during the Go/No-go task were recorded to provide brain activity data. Pain perception was assessed with the cold pressor test, in which subjects were asked to resist pain as long as possible. The exposure time (ET), intensity of tolerated pain and unpleasantness were interpreted as psychophysiological outcomes of pain.

Results: We observed that better performance on cognitive inhibition, assessed by Stroop interference tasks, was correlated with higher intensity of tolerated pain. Greater brain activity during response inhibition, evaluated as larger amplitude (P3), and shorter latency (N2) to a No-go stimuli were correlated with longer ET-pain tolerance.

Conclusions: In the healthy elderly, the neuronal circuits of cognitive inhibition and conscious pain control may overlap, and brain regions engaged in response inhibition may be more involved in behavioural response of pain.

1. Introduction

Pain has been found to be associated with cognition in older patients with chronic pain (Karp et al., 2008). In some studies, however, the direction of this association differed from that in younger patients. That is, most negative effects of pain on cognition are either no longer present or may even be reversed in older chronic pain patients. This suggests that aging affects brain structures involved not only in pain processing, but also in cognition (Oosterman et al., 2013). Considerable inter-individual variations in structural changes in frontal circuit and cognitive performance subtended by this cerebral region have been observed among older individuals (Moy et al., 2011; Lovden et al., 2013). However, the pain-related functional implications of this variability have yet to be determined (Farrell, 2012).

Evidence has suggested that ‘top-down’ control driven by the central nervous system is an important determinant of pain perception (Legrain et al., 2012). One down-regulation is related to conscious control, which is associated with activity in the ‘pain control center’, located in the prefrontal cortex (PFC; Salomons et al., 2007; Wiech et al., 2008). Also, deficits in executive functions have been observed in several chronic pain disorders, and performances on neuropsychological tests were significantly associated...
with subjective complaints of cognitive impairments and clinical pain ratings (Morarty et al., 2011). Thus, assessing the effects of PFC function on pain perception may contribute to the refinement of a neuropsychological model of pain (Jensen, 2011) and help in the development of more effective treatments.

Inhibition control, one important domain of executive function driven predominantly by the PFC, has been reported to be associated with pain in healthy subjects (Oosterman et al., 2010; Karsdorp et al., 2014). Executive control is related to the method by which an individual copes with pain, both cognitively (how the individual feels) and behaviourally (what the individual does), thus considered a key psychosocial domain for predicting the effects of both pharmacological and psychological treatments (Wich et al., 2008). This domain may be more important for elderly patients with chronic pain because they are less tolerant to invasive and pharmacologic therapies. Most previous studies of the association between inhibition and pain, however, were based on behavioural measures, which do not fully assess the underlying neural mechanisms.

This study therefore focused on investigating the relationship between inhibition functions and tonic pain perception in healthy elderly individuals. To investigate the relationship between pain and PFC function, we examined healthy participants to avoid a possible confounding relationship between cognition and chronic pain. The inhibition function was assessed by both neuropsychological (Stroop) tests and a typical inhibition response event-related potential (ERP) task (Go/No-go task) to evaluate behaviour and brain activity. Experimental pain was induced by the cold pressor task (CPT), which is considered a better model of clinical pain than phasic pain and is sensitive to psychophysiological responses (Chen et al., 1989). Mental flexibility and letter fluency were also evaluated and correlated with pain perception to provide a general view of PFC functions.

2. Materials and methods

2.1 Participants

We enrolled 29 healthy elderly volunteers (female/male = 15/14, 67.5 ± 5.6 years). None of the participants had a history of neurological or psychiatric disorders, or of abuse of alcohol or other substances. Educational level was rated according to GREFEX (Groupe de Réflexion sur l’Evaluation des Fonctions Exécutives) battery (Godefroy and Roussel-Pieronne, 2007) from 1 (less than primary school) to 5 (more than a bachelor’s degree). Subjects completed the French version (Marty et al., 1998) of the Dallas Pain Questionnaire, and all underwent medical examinations to exclude any individuals with chronic pain. The Mini-Mental State Examination was used to exclude subjects with cognitive impairments (i.e., total score < 27; Mungas, 1991). All participants were paid and provided informed consent prior to participation, in accordance with the guidelines of the local ethics committee, which approved the study.

2.2 Neuropsychological tests

Prefrontal lobe functions were assessed using the Stroop test, the Trail Making Test (TMT) and a letter fluency test from the GREFEX battery (Godefroy and Roussel-Pieronne, 2007). Cognitive inhibition was evaluated by Stroop interference scores (time Stroop Color Word card/time Stroop Color card). Mental flexibility and initiation/retrieval were assessed by the TMT-B-ratio score (time TMA part B/TMT part A) and the letter fluency test, respectively.

2.3 Pain perception assessment

Pain perception was determined using the cold pressor test (CPT). A cold air box with air temperature regulated at −5 °C (±1 °C) was used. The participants were instructed to keep their hand in the cold box as long as possible and keep their hand open and still. Subjects were to announce when pain was first sensed and to lift their arm out when the pain or unpleasantness became intolerable (von Baeyer et al., 2005). The times (in minutes) from exposure (ET) to the announcement of pain (ET-pain threshold) and to the withdrawal of the hand (ET-total) were recorded. ET-pain tolerance was calculated as ET-total minus ET-pain threshold (von Baeyer et al., 2005). Pain intensity/stimulus unpleasantness was assessed continuously (every minute) on a visual analogue scale (VAS) during exposure to maintain attention towards pain. Only the pain VAS rating of the minute preceding hand

What's already known about this topic?
- Prefrontal cortex (PFC) activity has been associated with cognitive modulation of both acute and chronic pain. Age-related decreases in cognitive function are also most pronounced in the PFC.

What does this study add?
- A significant positive correlation was found between inhibitory functions and experimental tonic pain tolerance in the healthy elderly. Performance on cognitive inhibition (Stroop test) was related to tolerated pain intensity while response inhibition evaluated by Go/No-go task was more correlated with behavioural pain response (time of pain tolerance).
withdrawal was used for analysis. Pain intensity was rated from 0 (no pain) to 100 (worst possible pain), and stimulus unpleasantness from 0 (not unpleasant) to 100 (extremely unpleasant). These pain outcomes were interpreted as psychophysiological outcomes of tonic pain, among which ETs were considered as behavioural response while intensity and unpleasantness were considered as conscious perception of pain. The lowest skin temperature was limited to 6 °C to avoid cold-induced injuries. The French version of the Fear of Pain Questionnaire – Short Form (Asmundson et al., 2008) was completed after CPT to reduce the impact of possible recall of the painful experience during CPT.

2.4 ERPs of the Go/No-go task

2.4.1 Task and procedures

Each trial began with a central fixed cross (+) presented for 400 ms, followed by the Go/No-go stimulus presented in the center of the screen for 400 ms. The Go (letter ‘F’) and No-go (Letter ‘E’) stimulus were displayed randomly with equal probability. The stimulus was replaced by a blank screen for a period of 1800 and 2200 ms (mean 2000 ms), within which the participants were required to respond, by pressing a button, to Go stimuli as fast as possible, or to refrain from responding to No-go stimuli. If participants did not press the button on Go trials (Omissions) or failed to press within 600 ms of stimulus onset (Outliers), or if they made incorrect responses (False Alarms), the related feedbacks appeared on the screen before the next stimulus to motivate the subjects to maintain attention and improve responses to the task.

Target Go/No-go stimuli, approximately 3 × 2 cm in size, were presented on a 17-inch computer monitor, with participants seated 70 cm from the screen in a quiet and dark room. Subjects were encouraged to keep eye movements and blinks to a minimum. The total number of test trials was 200.

2.4.2 Electrophysiological recording and analysis

Electroencephalography (EEG) was recorded from three midline sites (Fz, Cz, Pz) using an electrode cap containing Ag/AgCl electrodes fitted according to the international 10–20 system (BioSemi®, Amsterdam, the Netherlands). The EEG was digitized at 512 Hz, with an amplified band-pass of 0.1–100 Hz (including a 50 Hz Notch filter). Additional electrodes were placed on ear lobes as references (averaged offline). Vertical and horizontal electrooculographic potentials were recorded to reject ocular artefacts based on amplitude thresholds of ±100 μV from the analysis. All epochs were baseline corrected to 100 ms before the stimulus. The ERPs were averaged for each condition in epochs beginning 100 ms prior to stimulus onset and ending 1000 ms after the stimulus.

No-go effects (inhibition) were assessed by typical peak latency and amplitude measurements. The data were band-pass filtered (0.1–30 Hz) to attenuate the effects of noise on peak detection. It has been suggested that for the No-go condition, N2 components are maximal at the medial frontal and central sites and P3 components at midline electrodes for the elderly subjects (Lucci et al., 2013). We therefore limited the analyses to the Fz, Cz for N2 components and Fz, Cz, Pz sites for P3 components. The peak amplitudes and latencies were calculated for each subject in the time windows of 180–400 ms for N2 and 300–900 ms for P3.

2.5 Statistical analyses

For normally distributed data, the arithmetic mean and standard deviation of the mean were used as measures of central tendency and variability, whereas asymmetrically distributed data are represented by medians and skewness values. Neuropsychological test scores were standardized as z-scores and multiplied by –1 when necessary so that a higher score always represented a better performance. EP components between the Go and No-go tasks were compared using T-tests. Considering the skewed distribution of VAS pain ratings in the pain tolerance test, non-parametric correlation coefficients (i.e., Spearman correlation) were calculated between pain perception data and cognition data. ET-tolerance is normally distributed, thus Pearson correlation was used. Bonferroni corrections to the significance level were made for factors with more than two modalities (e.g., ERP data for multiple sites). Independent factors, such as the neuropsychological test results, did not require Bonferroni corrections for multiple correlations, so the common p-level (<0.05) was used. For all correlational analyses, those tests that revealed (marginally) significant associations with the pain perception variables were considered for further regression analyses.

Age, education, sex, depressive and anxious conditions and fear of pain may all significantly influence pain perception. To examine the potential contribution of these variables, correlations with pain perception measurements were calculated (including a point biserial correlation (rpb) with regard to sex). We controlled for those confounders that revealed a significant correlation with the pain, and retested the contributing effect of inhibitory functions by standard multiple linear regression analyses.

3. Results

3.1 Subjects and behavioural data

The demographics of the study participants, as well as the results of the CPT, neuropsychological examinations and questionnaires, are presented in Supporting Information Table S1.

One participant reported no pain but extreme unpleasantness at the limiting hand skin temperature (i.e., 6 °C). Two participants immersed their hands for less than 2 min in the cold box and did not likely
experience substantial pain prior to withdrawal. Thus these subjects were excluded from further analyses and a total of 26 participants were included.

### 3.2 ERP data

Fig. 1 shows the averaged waveforms for Go and No-go trials at the Fz, Cz and Pz electrodes.

ERP results are summarized in Supporting Information Table S2. The N2 peaked significantly earlier for Go than No-go stimuli (242.8 vs. 266.2 ms; \( t = -2.98; p = 0.004 \)) at the frontal site (Fz). N2 amplitude at the Fz site tended to be larger for No-go (0.16 \( \mu \)V) than for Go (1.68 \( \mu \)V; \( t = 1.67; p = 0.095 \)). The P3 amplitude had a parietal maximum in Go condition and a more anteriorly distribution (central-parietal) in No-go condition. That is, P3 amplitude was significantly larger in No-go than Go stimuli at Cz (11.28 vs. 8.12 \( \mu \)V; \( t = -2.65; p = 0.01 \)). P3 latency was significantly longer for No-go than for Go stimuli at the frontal site (450.0 vs. 401.8 ms; \( t = -3.37; p = 0.001 \)). These findings were in agreement with the results of previous ERP studies, indicating that the inhibitory (No-go) effect was significantly elicited (Pfefferbaum and Ford, 1988; Falkenstein et al., 1999; Bokura et al., 2001; Benikos et al., 2013).

### 3.3 Spearman correlation analysis

#### 3.3.1 Pain perception and neuropsychological tests

Stroop interference showed a significant positive correlation with perceived intensity of longest tolerated pain (\( R = 0.48; p = 0.014 \); Table 1, Fig. 2A), indicating that better performance on Stroop interference tests was related to a higher tolerance of perceived cold pain. No correlation was observed between ET-pain threshold and Stroop performance, confirming that Stroop performance is related to pain tolerance rather than sensitivity. Stroop interference score was not significantly correlated with stimulus unpleasantness, and the other PFC-related function performances were not correlated with CPT performance.

#### 3.3.2 Pain perception and Go/No-go tasks

Brain activity elicited by Go/No-go tasks showed a significant correlation between the No-go effect and psychophysiological pain outcomes (Table 1). The latency of No-go N2 was negatively correlated with ET-pain tolerance (N2: Fz \( R = -0.39; p = 0.049 \), Fig. 2B). In addition, the No-go P3 amplitudes at Cz (\( R = 0.39; p = 0.058 \), Fig. 2C) and Pz (\( R = 0.50; p = 0.009 \), Fig. 2D) were positively correlated with ET-pain tolerance, suggesting that greater No-go brain activity (i.e., shorter latency and higher amplitude) was
Table 1  Correlations of pain perception induced by CPT.

<table>
<thead>
<tr>
<th>No-go ERPs</th>
<th>ET-pain threshold</th>
<th>ET-pain tolerance</th>
<th>Pain intensity</th>
<th>Stimulus unpleasantness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fz No-go N2 L</td>
<td>−0.13</td>
<td>−0.39*</td>
<td>−0.08</td>
<td>0.18</td>
</tr>
<tr>
<td>Cz No-go N2 L</td>
<td>0.12</td>
<td>−0.22</td>
<td>−0.25</td>
<td>0.11</td>
</tr>
<tr>
<td>Fz No-go N2 A</td>
<td>0.14</td>
<td>0.11</td>
<td>0.22</td>
<td>−0.08</td>
</tr>
<tr>
<td>Cz No-go N2 A</td>
<td>−0.06</td>
<td>−0.02</td>
<td>0.31</td>
<td>−0.14</td>
</tr>
<tr>
<td>Fz No-go P3 L</td>
<td>0.12</td>
<td>−0.12</td>
<td>0.04</td>
<td>−0.26</td>
</tr>
<tr>
<td>Cz No-go P3 L</td>
<td>0.21</td>
<td>−0.02</td>
<td>−0.18</td>
<td>−0.30</td>
</tr>
<tr>
<td>Pz No-go P3 L</td>
<td>−0.02</td>
<td>−0.10</td>
<td>−0.05</td>
<td>−0.06</td>
</tr>
<tr>
<td>Fz No-go P3 A</td>
<td>−0.28</td>
<td>0.22</td>
<td>−0.07</td>
<td>0.09</td>
</tr>
<tr>
<td>Cz No-go P3 A</td>
<td>−0.04</td>
<td>0.39</td>
<td>−0.03</td>
<td>0.26</td>
</tr>
<tr>
<td>Pz No-go P3 A</td>
<td>0.09</td>
<td>0.50**</td>
<td>0.22</td>
<td>−0.10</td>
</tr>
</tbody>
</table>

Neuropsychological tests

<table>
<thead>
<tr>
<th>Stroop interference</th>
<th>0.20</th>
<th>0.20</th>
<th>0.48**</th>
<th>0.08</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMT-B/A</td>
<td>−0.09</td>
<td>−0.09</td>
<td>−0.10</td>
<td>0.05</td>
</tr>
<tr>
<td>Letter fluency</td>
<td>0.26</td>
<td>0.26</td>
<td>0.31</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Demography

| Age                | −0.26| −0.23| −0.18  | 0.15       |
| Sex                | −0.24| −0.27| −0.19  | −0.19      |
| Education          | −0.30| −0.18| 0.02   | 0.08       |
| BDI                | 0.07 | −0.02| −0.23  | −0.03      |
| STAI-S             | 0.07 | −0.26| −0.36* | −0.04      |
| STAI-T             | −0.10| −0.26| −0.34* | −0.24      |
| FPQ                | −0.38*| −0.17| 0.05   | −0.17      |

A, amplitude; BDI, Beck Depression Inventory; CPT, cold pressor test; ET, exposure time (min); FPQ, Fear of Pain-Short Form; L, latency; STAI-S, State-Trait Anxiety Inventory – State; STAI-T, State-Trait Anxiety Inventory – Trait; TMT, Trail Making Test.

Significant levels have been determined after Bonferroni correction as a function of number of comparisons:

*Significant tendency: 0.025 < p < 0.066 for N2; 0.016 < p < 0.033 for P3; 0.05 < p < 0.1 for all the rest data.

**Significance: p < 0.025 for N2; p < 0.016 for P3; p < 0.05 for all the rest data.

Figure 2  Scatterplots of the relationship between inhibition functions and pain perception outcomes. (A) Relationship between Stroop interference and pain intensity. Stroop interference score were normalized using z-score, and a higher neuropsychological score represents better performance. Pain intensity was scored from 0 (no pain) to 100 (worst possible pain). (B) Relationship between the latency of the P3 component (ms) to a No-go stimulus and exposure time (ET)-pain tolerance (minutes), at scalp sites Fz. (C) Relationship between the amplitude of the P3 component (μV) to a No-go stimulus and ET-pain tolerance, at scalp sites Cz. (D) Relationship between the amplitude of the P3 component (μV) to a No-go stimulus and ET-pain tolerance at the Pz site.
significantly related to longer pain tolerance time. No correlations between pain thresholds and ERP data were observed.

### 3.3.3 Multiple linear regression analysis

The confounder variables significantly associated with CPT performance are shown in Table 2. Regression analyses revealed that, after controlling for STAI-S and STAI-T, the contribution of Stroop interference to pain intensity was still significant ($\beta = 0.47; p = 0.012$; total $R^2 = 0.345$).

### 4. Discussion

This study showed that in elderly subjects, pain tolerance is correlated with inhibition functions. Better performance on the Stroop was related to tolerance of higher pain intensity and a greater inhibition response elicited by a Go/No-go task was associated with a longer time of tolerating pain. To our knowledge, this is the first study to investigate neural correlates of inhibition and pain perception using measurements of ERPs in healthy elderly individuals.

We used the two inhibition-related tasks to investigate inhibitory functions. Interestingly, we observed that Stroop interference performance and ERP components correlated differently with CPT pain outcome measures. That is, Stroop was related to tolerated pain intensity, while No-go ERP components were related to ET-pain tolerance. Despite their functional similarity, the cognitive process assessed by the two tasks is not the same. Go/No-go task performance may more accurately reflect response inhibition, which is related to activation in the middle and inferior frontal cortices (Bokura et al., 2001), pre-supplementary areas (pre-SMA) and the anterior cingulate cortex (ACC; Gonzalez-Rosa et al., 2013). Activation of the core inhibitory network and parietal areas increased with increasing age (Sebastian et al., 2013). The Stroop task may additionally measure informational conflicts inhibition, which is dissociable from response inhibition (Kalanthroff et al., 2013). This cognitive inhibition has been related to activation in a variety of PFC regions, and older adults appeared to use multiple frontal regions to a greater degree than younger adults (Langenecker et al., 2004; Zysset et al., 2007). Inhibition-related inter-task correlations (e.g., Stroop and Go/No-go tasks) have been reported to be few and weak in elderly individuals, but moderate in younger subjects, suggesting that the construct of inhibition may be multiform in aging (Rush et al., 2006). This difference may be explained by the compensatory hypothesis of aging (Reuter-Lorenz and Cappell, 2008), and result in different correlations with pain. Regarding pain-related brain activity, ACC, pre-SMA and the bilateral anterior insula were significantly stronger following the stimulation of C nociceptors (related to second pain) (Qiu et al., 2006), whereas the PFC is not involved in experimental pain perception but in pain control (Salomons et al., 2007). This may explain the different correlations: Go/No-go with ET-pain tolerance and Stroop with pain intensity.

The functional meanings of different components in the Go/No-go task may provide further information on the two sub-processes of response inhibition. The No-go N2 may reflect a pre-motor ‘need’ for inhibition or response conflict (Lucci et al., 2013). The No-go P3 has been more consistently interpreted as reflecting both cognitive and motor inhibition, which results in the effectiveness of behavioural inhibition (Smith et al., 2008). We observed that pain tolerance was only correlated with N2 Fz latency, while more correlations were found with P3 activity. The lack of correlation between No-go N2 and pain may be related to the low difficulty of our Go/No-go task. Indeed, its difficulty was probably not high enough to generate a pronounced No-go N2 amplitude (Benikos et al., 2013). Nevertheless, our results provide evidence that the N2 and P3 components are associated with pain tolerance, with the process represented by the P3 component being more strongly related to pain tolerance. Further studies using tasks of different difficulty are required to verify the involvement of the early conflict detection process in response inhibition of pain.

The present study focused on elderly individuals. Increasing age is associated with trends towards increased pain thresholds and decreased tolerance (Gibson and Farrell, 2004). This age-related limitation in pain range has been associated with deficiencies at both the peripheral and central levels, for instance, dysfunction of nociceptive nerve fibers (Kemp et al., 2013).
2014) and deficits in endogenous pain inhibition, which are related to activities of periaqueductal grey (PAG) and PFC (Lautenbacher, 2012). These age-related alterations at different levels of the pain pathway may contribute to altered pain tolerance in the elderly. The present study included only older adults as study subjects, thus minimizing age-related within-subject differences in peripheral pain pathways. However, the lack of quantitative assessment of peripheral pain pathway prevented the precise control of the individual differences within this age group. Nevertheless, in the absence of evidence for variability in peripheral pain pathways among older individuals, our correlation results suggest a central level mechanism.

Using elderly subjects only, we could not directly investigate age-related differences in the central mechanism of pain modulation. However, our findings provide evidence for the important role of PFC functioning in pain modulation in healthy older adults, at the levels of both behavioural and brain activities. We tentatively hypothesize that age-related deficiencies in PAG-mediated endogenous analgesia may be related to the deficit in top-down influence driven by the PFC. Hence, age-related deteriorations in inhibition at the cortical level also contribute to the deficit in pain inhibition in physiological aging. Clinically, this lack of pain inhibition may result in higher rates of pain complaints and symptoms in older subjects. Recent fMRI studies have shown that functional connectivity of PFC can predict the transition from acute to chronic pain in patients with subacute pain (Mansour et al., 2013), suggesting that PFC aging may increase, at least in part, the risk of pain chronicization in the elderly population. Further studies are required to test these hypotheses. For example, longitudinal coherence studies designed to assess the causal relationship between higher prevalence of chronic pain and inhibitory deficits in aging are needed. Altered pain perception has also been reported in older patients with cognitive impairment. However, despite the availability of numerous validated pain measures, pain remains poorly assessed in these patients, particularly in those with dementia (Karp et al., 2008). It is more challenging to study the relationship between altered pain perception and impaired cognitive function in patients with cognitive impairment. Studies of patients with mild cognitive impairment may minimize the impact of pain expression.

In summary, the results of the present study suggest that the brain regions engaged in response inhibition may also be involved in behavioural response of pain perception, and that cognitive inhibition and pain control may have overlapping neural circuits. The age-related limitations in pain range (higher sensitivity and lower tolerance) may be due in part to inhibition control deficits in older adults. Since inhibitory function is a fundamental executive function and may be a mechanism underlying non-pharmacological treatments (e.g., hypnosis, meditation), greater understanding will lead to a more complete neuropsychological model for chronic pain patients and the ability to tailor pain management individually.

Author contributions


References


Inhibition and pain in aging

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Additional Supporting Information may be found in the online version of this article at the publisher’s web-site:

**Table S1.** Characteristics of the participants (n = 26).

**Table S2.** Descriptive data (mean and standard deviation) and results of t-test on ERP (latency and amplitude) measurements for different condition in Go/No-go task.