Does cognitive functioning predict chronic pain? Results from a prospective surgical cohort

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It is well established that chronic pain impairs cognition, particularly memory, attention and mental flexibility. Overlaps have been found between the brain regions involved in pain modulation and cognition, including in particular the prefrontal cortex and the anterior cingulate cortex, which are involved in executive function, attention and memory. However, whether cognitive function may predict chronic pain has not been investigated. We addressed this question in surgical patients, because such patients can be followed prospectively and may have no pain before surgery. In this prospective longitudinal study, we investigated the links between executive function, visual memory and attention, as assessed by clinical measurements and the development of chronic pain, its severity and neuropathic symptoms (based on the ‘Douleur Neuropathique 4’ questionnaire), 6 and 12 months after surgery (total knee arthroplasty for osteoarthritis or breast surgery for cancer). Neuropsychological tests included the Trail-Making Test A and B, and the Rey-Osterrieth Complex Figure copy and immediate recall, which assess cognitive flexibility, visuospatial processing and visual memory. Anxiety, depression and coping strategies were also evaluated. In total, we investigated 189 patients before surgery: 96% were re-evaluated at 6 months, and 88% at 12 months. Multivariate logistic regression (stepwise selection) for the total group of patients indicated that the presence of clinical meaningful pain at 6 and 12 months (pain intensity ≥ 3/10) was predicted by poorer cognitive performance in the Trail Making Test B (P = 0.0009 and 0.02 for pain at 6 and 12 months, respectively), Rey-Osterrieth Complex Figure copy (P = 0.015 and 0.006 for pain at 6 and 12 months, respectively) and recall (P = 0.016 for pain at 12 months), independently of affective variables. Linear regression analyses indicated that impaired scores on these tests predicted pain intensity (P < 0.01) and neuropathic symptoms in patients with pain (P < 0.05), although the strength of the association was less robust for neuropathic symptoms. These results were not affected by the type of surgery or presurgical pain, similar findings being obtained specifically for patients who initially had no pain. In conclusion, these findings support, for the first time, the notion that premorbid limited cognitive flexibility and memory capacities may be linked to the mechanisms of pain chronicity and probably also to its neuropathic quality. This may imply that patients with deficits in executive functioning or memory because of cerebral conditions have a greater risk of pain chronicity after a painful event.
Introduction

The experience of pain is a complex phenomenon reflecting the interplay of many factors, including cognitive function (Apkarian et al., 2009; Oosterman et al., 2010a). Several studies have established that phasic experimental pain, such as that induced by electrical stimulus in healthy subjects, can impair performance on cognitive tasks particularly sustained selective attention and memory ( Crombez et al., 1996, 1997; Lorenz and Bromm, 1997). Furthermore it has been shown repeatedly that chronic pain may have a deleterious impact on attention, working memory, learning and memory, processing speed and executive function including cognitive flexibility ( Apkarian et al., 2009; Mioriarty et al., 2011 for reviews). Conversely attention demanding tasks or distraction from pain may have a modulatory effect on pain processing in healthy subjects ( Hodes et al., 1990; Eccleston, 1995; Wiech et al., 2005; Legrain et al., 2011; Verhoeven et al., 2011) and on clinical pain ( Eccleston, 1995; Sharpe et al., 2012).

Although the precise mechanisms involved in pain-related cognitive impairment have yet to be elucidated, one traditional concept, consistent with the load theory of attention ( Lavie, 2005), is that such impairment results mostly from hypervigilance to pain, with the patients focusing their attentional resources on coping with pain, thus reducing their ability to perform complex cognitive tasks ( Eccleston and Crombez, 1999; Legrain et al., 2009; Lautenbacher et al., 2010). Functional imaging studies have in fact revealed a significant overlap between the brain regions involved in cognition and pain modulation, including in particular the prefrontal cortex, which is involved in decision-making and executive function ( Miller and Cohen, 2001), and the anterior cingulate cortex, which is involved in selective attention and memory ( Seminowicz and Davis, 2007; Apkarian et al., 2009; Oosterman et al., 2010a; Mioriarty et al., 2011). This suggests that these areas may have reciprocal modulatory effects ( Bulhler and Wager, 2010). Interestingly these areas have also been implicated in mood and anxiety disorders ( Price and Drevet, 2012), both of which are frequently comorbid with chronic pain. Other studies have also reported neuroplastic and brain morphology changes associated with chronic pain ( Apkarian et al., 2004; Metz et al., 2009; Tracey and Bushnell, 2009; Baliki et al., 2011, 2012; Mutso et al., 2012), particularly in the dorso lateral prefrontal cortex ( Apkarian et al., 2004, 2009; Baliki et al., 2011). The pattern of change seems to differ between various types of pain, particularly between neuropathic and non-neuropathic pain ( Apkarian et al., 2004). This is consistent with recent studies showing that neuropathic pain is more debilitating than non-neuropathic pain ( Attal et al., 2011).

Altogether these data suggest that individual premorbid dysfunction of memory, attention or cognitive flexibility, suggesting differences in prefrontal cortex functioning and/or corticolimbic circuitry, play a role in the development of chronic pain, including neuropathic pain ( Solberg Nes et al., 2009; Williams, 2010; Lavandhome, 2011). Interestingly a recent human brain imaging study showed that the transition from acute to chronic pain after an episode of acute low back pain could be predicted by functional connectivity between the striatum and the prefrontal cortex ( Baliki et al., 2012). However, clinical tools have never been used to assess prospectively the predictive role of cognitive flexibility, attention or memory in the development of chronic pain in patients.

Chronic postoperative pain is a particularly suitable clinical condition for the exploration of this question, because patients can be followed longitudinally and many have no pain before surgery ( Kehlet et al., 2006). We have previously shown that measures of anxiety and catastrophizing (amplification) could predict the transition from acute to chronic pain at 3 months in two distinct surgical models: total knee arthroplasty for osteoarthritis, a benign intervention mostly carried out in elderly people suffering from chronic preoperative pain and; breast cancer surgery, mostly in younger females with little or no preoperative pain ( Masselin-Dubois et al., 2013). The main objective of the present study was to investigate the link between executive function, visual memory and attention, as assessed by clinical measurements and the development of chronic pain and its severity 6 and 12 months after surgery in these surgical models. We hypothesized that it might be possible to detect predictive neuropsychological risk factors common to these surgical models, despite their heterogeneity. As a number of studies have pointed to the predictive value of anxiety, depression or coping on chronic post-surgical pain ( Hinricks-Rocker et al., 2009; Theunissen et al., 2012), we also investigated the possible contribution of these variables to pain prediction. Finally, as these surgical models also induce different types of pain (mostly non-neuropathic in the knee arthroplasty model and neuropathic in the breast surgery model), we assessed whether neuropsychological variables predicted neuropathic characteristics in these surgical models.

Materials and methods

Participants and procedure

The study sample consisted of two groups of patients undergoing total knee arthroplasty or breast cancer surgery, recruited between May 2008 and June 2011. Data regarding the predictive value of anxiety and catastrophizing on the transition from acute to chronic pain at 3 months in the same sample of patients have been previously published ( Masselin-Dubois et al., 2013). The study was approved by the local ethics committee ( CPP Ile de France VIII ) and all patients gave informal consent.

Total knee arthroplasty patients were recruited from Raymond Poincaré Hospital ( Garches, APHP). Eligible patients were males and females aged 18 to 85 years, scheduled for unilateral arthroplasty for osteoarthritis of the knee. Patients were not included if they suffered from conditions other than osteoarthritis necessitating arthroplasty...
(i.e. rheumatoid arthritis, spondylarthropathy), required bilateral arthroplasty or had undergone previous knee surgery. Surgery was performed in the same surgical ward in each case, by one of three highly experienced surgeons, in an identical, standardized protocol, as reported previously for these patients (Masselin-Dubois et al., 2013). The anaesthetic procedure was similar for all patients and combined propofol, sufentanil, a muscle relaxant and sevoflurane. In all patients, postoperative pain was controlled by intravenous patient-controlled morphine analgesia together with intravenous acetaminophen, ketoprofen and a femoral peripheral nerve block. At follow-up visits at 6 and 12 months, all the radiographic data confirmed that all implants were well aligned mechanically and that implant placement was satisfactory.

The second group of patients consisted of females aged 18 to 85 years recruited from Rene Huguenin Hospital (Saint Cloud, lIe de France) for mastectomy or lumpectomy to treat breast cancer, with axillary lymph node dissection in all cases. No patient underwent breast reconstruction during the whole observation period. Surgery was performed in the same surgical ward in each case, by one of five surgeons, according to an identical procedure. The surgeon had no significant impact on the prevalence of pain at 6 and 12 months after breast surgery (the prevalence of clinical meaningful pain according to the surgeon ranged from 16% to 20% at 6 months and 16% to 21.1% at 12 months, P > 0.7). The type of surgery (lumpectomy or mastectomy) had no impact on the prevalence of pain and data for these two procedures were therefore analysed together. Females were not included if they had a history of previous surgery of the thoracic or cervicobrachial region, including prior mastectomy or lumpectomy, were scheduled for lumpectomy for a benign tumor, for bilateral mastectomy or for a second breast surgery procedure during the 3 months of follow-up, had other malignant conditions or evidence of distant metastases (apart from lymph node macrometastases), had undergone radiotherapy or chemotherapy before surgery or had clinically relevant pain (> 3/10) before surgery. Data for radiotherapy and chemotherapy during the 6 and 12 months following surgery were obtained from the patients’ medical reports. The anaesthetic procedure was similar for all patients and has been described elsewhere (Masselin-Dubois et al., 2013): general anaesthesia was induced with propofol, sufentanil and atracurium or cisatracurium, to facilitate orotracheal intubation. Postoperative pain was controlled by intravenous acetaminophen.

All the patients in both surgical groups were native French speakers. We did not include patients with clinically significant or unstable psychiatric or somatic conditions (e.g. major depression, psychosis, uncontrolled diabetes mellitus or hypertension, neurological disorders, immune disease, body mass index > 45), past or present substance abuse or any cognitive deterioration based on past medical history, semi-structured interview and lack of completion or full understanding of questionnaires. All assessments were performed in the presence of a certified psychologist. Data regarding demographic variables, neuropsychological tests, pain-related cognition, trait anxiety and coping strategies were obtained 1 month before surgery, whereas information about pain, state anxiety and depression, were obtained 1 day before surgery. However, as patients from the breast group had no presurgical pain, the two questionnaires related to pain-related coping strategies and control over pain (see below) were administered 2 days after surgery as these questionnaires have been validated for use only in patients with pain. All patients were questioned again about their postsurgical pain status through postal surveys 6 and 12 months after surgery. The level of missing data was minimized by the investigators contacting those who did not return their pain evaluation, directly by telephone, after each postal survey.

### Measurements

#### Postoperative pain

Identical questionnaires were used to assess postoperative pain in the area treated in the two surgical groups, to ensure that the results obtained were comparable. Average pain intensity over the past week (on a numerical scale from 0: no pain, to 10: the worst pain you can imagine) was assessed preoperatively and postoperatively at 6 and 12 months, with the Brief Pain Inventory (Cleeland and Ryan, 1994). Clinically meaningful pain was considered to be present if patients rated their average pain as ≥ 3/10. This cut-off corresponds to at least moderate pain with a potential impact on physical or emotional functioning and has been commonly used in previous studies with similar prospective design (Poleshuk et al., 2006; Thyregod et al., 2007; Masselin-Dubois et al., 2013).

The seven-item version of the DN4 questionnaire (Douleur Neuropathique en 4 questions) (Bouhassira et al., 2005), which includes questions relating to typical neuropathic symptoms (e.g. burning, painful cold, electric shocks, tingling, pins and needles, numbness, itching), each scored as present (1) or absent (0), was used for patients with pain. We did not apply the cut-off score (≥ 3/7) to determine whether patients had or not neuropathic pain because the number of patients with neuropathic as compared to non-neuropathic pain was low. Rather we used the DN4 score as a continuous variable to assess the number of neuropathic symptoms (from 0: no neuropathic symptoms; to 7: maximal number of neuropathic symptoms) (Attal et al., 2011).

#### Neuropsychological assessment

Patients underwent presurgical cognitive evaluation by the same certified neuropsychologist one month before surgery. The functions assessed included executive function (defined as a cluster of higher-order capacities, organization and planning, the ability to shift between sets of objects or concepts, response inhibition and the manipulation of information during problem solving), selective and divided attention (Lezak, 1995).

The following tests were used:

(i) The Rey-Osterrieth Complex Figure Test (ROCF), which includes three test conditions: Copy, Immediate Recall and Delayed Recall (Rey, 1941; Osterrieth, 1944). The two first conditions were used in this study. The subjects were initially asked to draw a complex figure and were subsequently (i.e. immediately after the copy) asked to draw what they remembered of that figure. The lower the score the higher the impairment. The ROCF-copy test assesses perceptive, visuospatial and constructional abilities, but also executive function (i.e. the strategies used by the individuals to draw the complex figure, organization and planning), whereas the ROCF-immediate recall test principally evaluates visual memory (Shin et al., 2006); and

(ii) The Trail-Making Test (TMT) (Reitan, 1958), which has two parts, A and B. Identical scanning, speed and motor responses are required in each part, but part B also requires the subject to be able to maintain two simultaneous sequences mentally, sustained attention and working memory, and cognitive flexibility (Crowe, 1998; Kortte et al., 2002; Sanchez-Cubillo et al., 2009; Salthouse, 2011). We used the score based on the time taken to complete each part of the test (in seconds). Higher scores indicate poorer performance in TMT. In the lack of a control group, data obtained on the TMT and ROCF were compared to commonly-used adult norms in French subjects paired for age and education.
Emotional functioning and coping

We assessed mood and anxiety before surgery, with two different tools, in both groups. The 13-item Beck Depression Inventory (Beck et al., 1961, 1996) was used to assess the presence and severity of depressive symptoms. For this scale, each item is scored on a four-point scale (0–3), with higher scores reflecting more severe symptoms (range 0–39). The standard cut-offs are as follows: 0–4: no depression; 4–7: mild depression; 8–15: moderate depression; and ≥16: severe depression (Beck et al., 1996).

The Spielberger State Trait Anxiety Inventory (20 items, range 20–80) was used to assess self-reported anxiety (Spielberger et al., 1983). A score ≥40 suggests the presence of anxiety (Spielberger et al., 1983).

The French validated adaptation of the Coping Strategies Questionnaire (Rosenstiel and Keefe, 1983) was used to assess pain coping strategies (Irachabel et al., 2008). This version consists of 21 items relating to five factors: distraction, catastrophizing, ignoring and reinterpreting pain sensations and praying. For each dimension, subjects are asked to rate items on a four-point scale (1 = never; 4 = very often). The factors ‘praying’ and ‘catastrophizing’ were grouped into a single domain defining passive coping strategies (scored 0 to 25), whereas the other three factors were grouped into a domain defining active coping strategies (scored 0 to 54). This questionnaire was completed 2 days after surgery for the women undergoing breast surgery.

The Control Scale from the Brief Version of the Survey of Pain Attitudes (Tait and Chibnall, 1997) was used to assess perception of control over pain and ability to influence the amount of pain experienced. It includes five items, each rated on a five-point scale (0: very untrue; 4: very true, scored 0 to 20). This scale was administered 2 days after surgery for the females undergoing breast surgery.

Statistical analysis

Descriptive statistics were used to analyse the demographic and clinical characteristics of the sample. Student’s t-tests were used to compare presurgical quantitative variables (e.g. demographic, clinical and neuropsychological and affective data) between patients who did and did not develop chronic pain by 6 and 12 months because the assumptions (normality and equality of variance in the populations) underlying its utilization were verified, while corrected χ² tests were used for categorical variables. Wilcoxon tests were used to compare patients before and after surgery because the change of scores from baseline did not have a gaussian distribution in this population (Armitaihe et al., 2002).

In line with previous prospective studies of pain prediction (Peters et al., 2007; Gartner et al., 2009; Bouhassira et al., 2012; Masselin-Dubois et al., 2013) we conducted multivariate logistic and linear regression analyses (Gnanadesikan and Kettenring, 1984) to identify predictors of chronic pain prevalence and intensity at 6 and 12 months. Contrary to univariate analyses, regression analyses take into account the intercorrelations between variables and avoid type 1 errors inflation. We used the terms ‘predictors’ for variables considered at entry in multivariate regression models, while ‘independent predictors’ referred to variables found significantly predictive of the outcome after testing (Draper and Smith, 1998). The use of the term ‘independent predictor’ was justified by the fact that in regression models the contribution of a significant predictor to the outcome is mathematically independent of the contributions of the other predictors (Draper and Smith, 1998).

Several regression analyses were performed to identify independent predictors of pain prevalence or intensity at 6 and 12 months. We first conducted logistic regression analyses on the total sample of patients from both surgical groups then on each surgical group, to identify independent predictors of the presence of clinically meaningful pain at 6 and 12 months (based on a score ≥3/10 on the Brief Pain Inventory). Linear regression analyses were also conducted on the total sample then on each surgical group, to identify independent predictors of postsurgical pain intensity (with average pain intensity on the Brief Pain Inventory treated as a continuous variable). Finally linear regression analyses were conducted with the same statistical models in the sample of patients with pain from both surgical models, to identify independent predictors of the number of neuropsychic symptoms, as assessed by the DN4 questionnaire.

For each logistic regression and multiple regression analysis we used a stepwise selection procedure as an exploratory approach (Tabachnik and Fidell, 2007), as follows.

Clinical selection of variables (predictors)

Variables included the type of surgery (breast, total knee arthroplasty), sex (male or female), age (as a continuous variable), preoperative pain intensity (as a continuous variable in the arthroplasty group), radiotherapy or chemotherapy (yes/no, in the breast surgery group), affect/cognition evaluations (Beck Depression Inventory, Spielberger State Trait Anxiety Inventory, active and passive coping strategies of the Coping Strategies Questionnaire, Control scale of the Survey of Pain Attitudes, as continuous variables) and results of neuropsychological tests (TMT A and TMT B, ROCF-copy and ROCF-immediate recall, as continuous variables). Neuropsychological variables were also entered as dichotomous variables in additional analyses based on currently used normative values paired for age and education (Fastenua et al., 1999; Tomhau, 2004). To avoid biased results due to the lack of consideration of confounding variables, the choice of affective and somatic variables was based on findings of previous studies showing their clinical relevance to predict acute or chronic pain (Peters et al., 2007; Pinto et al., 2012; Masselin Dubois et al., 2013). Spearman’s correlations (Rho) were also calculated among study variables to determine the predictor variables to be entered in the multivariate models (Tabachnik and Fidell, 2007).

Statistical selection of variables

Univariate analyses: These analyses examined a significant relationship between each of the above variables and each dependent variable (presence or intensity of pain at 6 and 12 months). These variables were entered into multivariate regression analyses if they were judged to be of high clinical significance (e.g. age, sex, surgical model) or were found to distinguish between patients with and without pain in univariate analyses, with a liberal significance level of P < 0.20 in all cases. This liberal set of criteria has been recommended in applied
logistic regression (Affi and Azen, 1979; Hosmer et al., 2013) and commonly used in similar prospective studies (Katz et al., 2005; Poleschuk et al., 2006; Peters et al., 2007).

Stepwise selection and multivariate analyses: In the stepwise selection, predictors were added one by one to the regression model if they met statistical criteria, but could be deleted at any step if they no longer contributed significantly to the regression. At each step, a different model was automatically built and tested. This model was improved until the final model considered as containing the best predictors was obtained, based on the statistical criteria chosen. In the presentation of results, the order of predictors was that automatically generated by the stepwise selection regression procedure.

To control for the influence of multi-collinearity, we calculated the tolerance (or variance inflation factor) of all variables included in the final linear models. They were in each case >0.71 for pain at 6 months and >0.56 for pain at 12 months, showing no collinearity between covariates. Residuals were plotted (i) as quantile-quantile plots; and (ii) as a function of predicted outcome values (residual plots) for each final model: the points were close to the Q–Q line and no particular tendency was noticed in the residual to predicted cluster of points, thus the hypothesis of homoscedasticity was deemed acceptable (Supplementary material). In addition, potentially pertinent interactions in our analyses were tested. Namely they were first order interaction terms between the group variable (surgical procedure) and interactions in our analyses were tested. Namely they were first order acceptable (Supplementary material). In addition, potentially pertinent cluster of points, thus the hypothesis of homoscedasticity was deemed acceptable (Supplementary material). In addition, potentially pertinent cluster of points, thus the hypothesis of homoscedasticity was deemed acceptable (Supplementary material).

Statistical analyses were performed by an independent statistician (C. Fermanian) using SAS/STAT 9.1 (SAS Institute). Missing data were not imputed. We considered P-values < 0.05 to be significant.

Results

Patient characteristics

The flow chart for these patients has been reported elsewhere (Masselin-Dubois et al., 2013). Briefly, 427 consecutive patients scheduled to undergo total knee arthroplasty or breast cancer surgery were asked to participate in the study: 104 declined to participate and 76 were ineligible (essentially because of significant medical/psychiatric comorbidity, language difficulties, cognitive disorders or age >85 years). In total, 264 subjects provided informed consent, of who 75 were subsequently excluded (refusal to undergo the entire series of tests, cancellation of surgery, major cognitive deterioration, non-native French speaker or impairment of one or more senses (hearing or vision) detected during testing). The surgical sample thus consisted of 189 patients undergoing arthroplasty (n = 89 patients, 65% female, mean age: 68.7 ± 8.9 years) or breast surgery [n = 100 females scheduled for breast mastectomy (64%) or lumpectomy (36%), mean age: 55.2 ± 12.1 years], with axillary node dissection carried out for both types of breast surgery (Table 1). These characteristics are consistent with those reported previously after total knee arthroplasty (Brander et al., 2003; Sullivan et al., 2011) or breast surgery (Katz et al., 2005; Poleschuk et al., 2006).

In total, 181 patients (96% of the sample) were reassessed at 6 months and 165 (88%) were assessed at 12 months. Most patients in the arthroplasty group (84%) had clinically meaningful presurgical pain (score ≥3/10). No patient from the breast group had clinically meaningful pain before surgery; two-thirds were treated postoperatively, before the assessments at 6 and 12 months, by radiotherapy (57% at 6 months, 76% at 12 months) or chemotherapy (62% at 6 months; 63% at 12 months), with the same protocol used in all cases (5-FU, epirubicin and cyclophosphamide every 3 weeks, followed by docetaxel). None of the females received hormone therapy during the follow-up period.

Table 1 shows the presurgical neuropsychological and affective characteristics of the patients undergoing surgery. As compared to published norms (Fastenau et al., 1999; Tomhaugh, 2004), the majority of patients had normal values before surgery. However, the proportion of impaired patients was significantly higher in the arthroplasty group as compared to the breast group as regards TMT A, B and ROCF-recall, probably because of older age, different sex ratio and the presence of chronic pain. Mean depression scores were in the normal range and similar between groups, with only two patients scoring above the threshold for severe symptoms (>16/39) and average values of the Spielberger anxiety scale suggested a moderate level of anxiety in both groups (Spielberger et al., 1983). These data are in line with findings obtained with the same scales in similar or other surgical samples of patients (Katz et al., 2005; Pan et al., 2006; Poleschuk et al., 2006). Only a few patients received psychotropic medication for sleep or anxiety, in the form of low-dose benzodiazepines and/or serotoninergic antidepressants (8% in the arthroplasty and breast cancer surgery groups). In the arthroplasty group, 63% received continuous analgesic medication for pain, mostly level I or II analgesics, but strong opioids were prescribed in exceptional cases (two patients).

In line with previous reports (Tomhaugh, 2004; Hester et al., 2005), neuropsychological performances on TMT were correlated with increasing age (Rho: 0.34 to 0.45 for TMT A in the arthroplasty and breast groups respectively; P < 0.01; Rho: 0.48 for TMT B in the breast model, P < 0.001) and inversely correlated with years of education (Rho: −0.45 for TMT A in the breast group, P < 0.001; Rho: −0.36 to −0.48 for TMT B in the total knee arthroplasty and breast group, respectively; P < 0.01). Moderate correlations were also observed between presurgical average pain intensity in arthroplasty patients and increased TMT time (Rho: 0.23 for TMT A and B; P < 0.05). Times on TMT A and TMT B were correlated in the total sample of patients (Rho: 0.70; P < 0.001), but neuropsychological variables were not or poorly correlated with depression or anxiety (Rho < 0.19 in all cases), suggesting a lack of multicollinearity. The only exception concerned passive coping strategies, which were moderately correlated to increased TMT B time (Rho: 0.25; P = 0.0007) and decreased score on ROCF-copy (Rho: −0.28; P < 0.0001). Thus, poorer cognitive performances were associated with higher scores for passive coping, suggesting maladaptive pain coping. Finally there was no relationship between neuropsychological performance and sex or the use of analgesic/psychotropic medication.

Postoperative pain outcome

The proportion of patients presenting clinically meaningful pain was 84% before surgery in the arthroplasty group and decreased
significantly after surgery (39% and 38% had clinically meaningful pain at 6 and 12 months, respectively) \((P < 0.001)\) (Table 2). This proportion was significantly higher than after breast surgery (no patient had pain prior to surgery in this group, and 20 and 18% of patients had clinically meaningful pain at 6 and 12 months, respectively) \((P < 0.001)\). Mean pain intensity in patients with pain decreased after arthroplasty, whereas it remained constant after breast surgery between 6 and 12 months (Table 2). The number of neuropathic symptoms in patients with pain at the 6- and 12-month visits was greater for breast surgery than for arthroplasty (Table 2).

**Univariate comparisons between patients with and without pain**

The presurgical performances of several neuropsychological tests (TMT B, ROCF-copy and recall) and the scores on affective variables (state anxiety, depression and passive coping) significantly differentiated patients who reported pain 6 and 12 months after surgery from painless patients in both surgical groups \((P < 0.05)\) (Table 3). Pain intensity before surgery distinguished between patients with or without pain at 6 months in the arthroplasty group \((P = 0.03)\) (Table 3). In contrast, neither the Survey of Pain Attitudes control scale nor active coping strategies differentiated between painful and painless patients while trait anxiety tended to be higher in painful patients in the breast group \((P = 0.07 \text{ to } 0.08)\).

**Predictors of the presence and severity of postsurgical pain in the total sample of patients**

Variables judged to be of clinical significance (age, sex, surgical group) or that distinguished between patients with and without pain in both surgical groups at 6 and 12 months with a liberal significance level of \(P < 0.20\) (Table 3) were entered in logistic

### Table 1 Demographic, clinical and psychological variables at baseline in the total knee arthroplasty and breast cancer surgery groups

<table>
<thead>
<tr>
<th></th>
<th>Total knee arthroplasty group ((n = 89))</th>
<th>Breast surgery group ((n = 100))</th>
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</thead>
<tbody>
<tr>
<td><strong>Clinical/demographics variables</strong></td>
<td></td>
<td></td>
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<tr>
<td>Sex (females/males) (%)</td>
<td>65/35***</td>
<td>100/0</td>
</tr>
<tr>
<td>Age</td>
<td>68.7 ± 8.9 (44–85)***</td>
<td>55.2 ± 12.1 (32–80)</td>
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<tr>
<td>Years of education</td>
<td>12.5 ± 4.4 (4–20)</td>
<td>11.7 ± 4.1 (4–20)</td>
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<tr>
<td>Psychotropic medication (%)</td>
<td>8</td>
<td>8</td>
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<tr>
<td><strong>Psychological variables</strong></td>
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<tr>
<td>Trait anxiety (20–80)</td>
<td>41.9 ± 8.1 (28–65) ((n = 88))</td>
<td>42.0 ± 9.2 (24–71)</td>
</tr>
<tr>
<td>Trait anxiety (%) (a)</td>
<td>56.8</td>
<td>55</td>
</tr>
<tr>
<td>State anxiety (20–80)</td>
<td>40.5 ± 12.3 (20–69) ((n = 88)***</td>
<td>45.8 ± 13.5 (21–79)</td>
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<tr>
<td>State anxiety (%) (a)</td>
<td>56</td>
<td>64</td>
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<tr>
<td>Beck Depression Inventory (0–39)</td>
<td>4.6 ± 3.9 (0–20)</td>
<td>3.8 ± 3.6 (0–18)</td>
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<tr>
<td>Depression (Beck) (%) (b)</td>
<td>50</td>
<td>44</td>
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<tr>
<td>Minor (%)</td>
<td>32</td>
<td>32</td>
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<tr>
<td>Moderate (%)</td>
<td>17</td>
<td>11</td>
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<tr>
<td>Severe (%)</td>
<td>1</td>
<td>1</td>
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<tr>
<td>CSQ coping active strategies</td>
<td>30.2 ± 7.3 (14–53)</td>
<td>30.3 ± 7.4 (17–54)</td>
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<tr>
<td>CSQ coping passive strategies</td>
<td>13.7 ± 4.2 (7–25)</td>
<td>13.4 ± 3.5 (7–21)</td>
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<tr>
<td>SOPA-B control scale</td>
<td>11.2 ± 4.2 (0–19)***</td>
<td>12.8 ± 3.6 (2–19)</td>
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<td><strong>Neuropsychological variables</strong></td>
<td></td>
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<tr>
<td>TMT A time (0–240)</td>
<td>60.5 ± 32.0 (20–236)***</td>
<td>40.6 ± 15.7 (12–89)</td>
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<tr>
<td>Impairment on TMT A (%) (c)</td>
<td>35**</td>
<td>12</td>
</tr>
<tr>
<td>TMT B time (0–240)</td>
<td>114.1 ± 50.1 (38–240) ***</td>
<td>74.3 ± 35.2 (18–185)</td>
</tr>
<tr>
<td>Impairment on TMT B (%) (c)</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>Score for ROCF-copy (0–36)</td>
<td>29.3 ± 6.4 (0–36) ((n = 87))</td>
<td>28.3 ± 4.9 (3–36)</td>
</tr>
<tr>
<td>Impairment on ROCF-copy (%) (d)</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>Score for ROCF-immediate recall (0–36)</td>
<td>13.7 ± 6.4 (0–32) ((n = 87))*</td>
<td>15.9 ± 6.2 (1–29)</td>
</tr>
<tr>
<td>Impairment on ROCF-recall (%) (d)</td>
<td>33***</td>
<td>11</td>
</tr>
</tbody>
</table>

Data are expressed as means ± SD (range).

\*\*\* \(P < 0.0001\); \*\* \(P < 0.01\); \* \(P < 0.05\) between groups (t-tests).

CSQ = Coping Strategies Questionnaire; SOPA = Survey of Pain Attitudes.

\(a\) Cut-off for at least mild anxiety was based on Spielberger recommended cut-off of 39.

\(c\) Cut-offs for depressive symptoms (Beck et al., 1996): mild depression: score 4–7; moderate depression: score 8–15; severe depression ≥16.

\(d\) Impaired patients deviated by >1.65 SD from mean normative values for TMT, paired by age and education (Tombaugh, 2004).

Differentiated patients who reported pain 6 and 12 months after surgery from painless patients in both surgical groups \((P < 0.05)\) (Table 3). Pain intensity before surgery distinguished between patients with or without pain at 6 months in the arthroplasty group \((P=0.03)\) (Table 3). In contrast, neither the Survey of Pain Attitudes control scale nor active coping strategies differentiated between painful and painless patients while trait anxiety tended to be higher in painful patients in the breast group \((P=0.07\text{ to }0.08)\).
Table 2 Development of pain (assessed with the Brief Pain Inventory) after surgery in the total knee arthroplasty and breast cancer surgery groups, at 6 and 12 months

<table>
<thead>
<tr>
<th></th>
<th>Baseline Arthroplasty* n = 89</th>
<th>6 months Arthroplasty n = 81</th>
<th>Breast Arthroplasty n = 100</th>
<th>12 months Arthroplasty n = 69</th>
<th>Breast Arthroplasty n = 96</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with clinically meaningful pain: n (%)</td>
<td>74 (84%)</td>
<td>32** (39.5%)</td>
<td>20 (20%)</td>
<td>26** (37.7%)</td>
<td>17 (17.7%)</td>
</tr>
<tr>
<td>Pain intensity in patients with pain, mean ± SD (range)</td>
<td>5.4 ± 1.5 (3–9) (n = 75)</td>
<td>4.4 ± 1.8 (3–9)** (n = 32)</td>
<td>4.3 ± 1.8 (3–9) (n = 20)</td>
<td>3.9 ± 1.1 (3–9)** (n = 26)</td>
<td>4.3 ± 1.9 (3–9) (n = 17)</td>
</tr>
<tr>
<td>Number of neuropathic symptoms in patients with pain, mean ± SD (range)</td>
<td>2.4 ± 1.7 (0–7) (n = 75)</td>
<td>2.4 ± 1.6 (0–7) (n = 32)</td>
<td>3.6 ± 1.7 (0–7) (n = 20)</td>
<td>2.1 ± 1.3 (0–7) (n = 26)</td>
<td>3.4 ± 1.4 (0–7) (n = 17)</td>
</tr>
</tbody>
</table>

*No patient reported chronic pain before surgery in the breast group.

**P < 0.001 for comparisons with presurgical values (Wilcoxon test for continuous variables, χ² for categorical variables).

The proportion of patients experiencing pain was significantly higher after total knee arthroplasty than after breast surgery, at 6 and 12 months (P < 0.001). Conversely, the number of neuropathic symptoms in painful patients was significantly lower in the arthroplasty group than in the breast group, at 6 months (P = 0.01) and 12 months (P = 0.005).

Table 3 Comparison of presurgical somatic and psychological variables in the total knee arthroplasty and breast surgery groups, between patients with and without pain at 6 and 12 months

| Presurgery characteristics | Total knee arthroplasty | 6 months | 12 months | | Breast surgery | 6 months | 12 months |
|----------------------------|-------------------------|----------|-----------| |                |          |           |
| Age                        | 69.2 (9.1)              | 68.0 (8.8) | 0.5       | 66.9 (8.5) | 69.7 (8.9) | 0.19 |
| Sex (women/men) %          | 78/22                   | 65/35    | 0.06      | 69/31      | 63/37     | 0.59 |
| Pain intensity             | 5.3 (1.9)               | 4.3 (2.3) | 0.03      | 5.4 (1.9)  | 4.5 (2.0) | 0.06 |
| State anxiety (20–80)      | 44.8 (13.4) (n = 31)    | 38.6 (11.1) | 0.03    | 43.4 (10.8) (n = 25) | 38.4 (12.6) | 0.10 |
| Trait anxiety (20–80)      | 42.6 (7.9)              | 42.1 (8.3) | 0.78      | 41.4 (7.6) | 41.7 (8.3) | 0.89 |
| Beck Depression (0–39)     | 6.4 (4.7) (n = 31)      | 3.7 (3.1) | 0.003     | 5.5 (4.0)  | 3.8 (3.2) | 0.07 |
| CSQ passive coping (0–25)  | 15.2 (4.5)              | 12.6 (3.8) | 0.006     | 15.3 (4.4) | 12.2 (3.5) | 0.002 |
| CSQ active coping (0–54)   | 30.6 (7.5)              | 29.9 (7.5) | 0.72      | 31.1 (8.4) | 30.3 (7.4) | 0.66 |
| TMT A time (0–240)         | 66.3 (40)               | 54.9 (25.9) | 0.12    | 62.9 (39.9) | 53.7 (24.9) | 0.24 |
| TMT B time (0–240)         | 137.9 (85.8)            | 103.4 (46.2) | 0.02   | 128.5 (56.9) | 98.3 (40.8) | 0.01 |
| ROCF copy (0–36)           | 28.7 (5.9) (n = 31)     | 30.8 (5.4) (n = 47) | 0.11 | 28.5 (6.4) | 31.5 (3.9) (n = 41) | 0.022 |
| ROCF recall (0–36)         | 12.4 (6.1) (n = 24)     | 14.7 (6.1) (n = 43) | 0.14 | 11.2 (5.2) (n = 19) | 16.0 (6.2) (n = 39) | 0.0077 |

Patients with and without pain were compared in Student’s t tests for continuous variables and corrected χ² tests for categorical variables. *Unless otherwise specified.

CSQ = Coping Strategies Questionnaire; SOPA = Survey of Pain Attitudes.
regression models (Table 4) and in linear regression models (Table 5) in the total sample of patients.

Logistic regression analyses (stepwise selection) indicated that the presence of clinical meaningful postsurgical pain (at 6 or 12 months) was significantly predicted by TMT B (P = 0.009 and 0.02 at 6 and 12 months, respectively), ROCF-copy (P = 0.015 and 0.006 at 6 and 12 months, respectively) and ROCF-immediate recall (P = 0.01 for pain at 12 months) (Table 4). In linear regression analyses (stepwise selection) (Table 5), TMT B time also significantly contributed to the prediction of pain severity at 6 and 12 months (P < 0.001) and ROCF-immediate recall contributed to the prediction of pain severity at 12 months (P = 0.005).

Regarding affective variables, state anxiety predicted the presence and severity of pain at 6 months but not 12 months, whereas depression score predicted the presence and severity of pain at 12 months only (Tables 4 and 5). Passive coping scales independently predicted the presence of pain at 12 months (P = 0.006) (Table 4). Neither surgical group nor age was significantly predictive of pain prevalence or intensity (Tables 4 or 5).

Thus the final statistical model of the stepwise selection retained both affective and neuropsychological variables as independent predictors of pain prevalence and intensity at 6 and 12 months, as further illustrated by Fig. 1.

When neuropsychological variables were expressed as dichotomous variables (based on their variations from published norms) in the logistic regression models, the odds for TMT B to develop pain at 6 and 12 months were 3.6 [95% confidence interval (CI): 1.3–10.2; P = 0.01] and 4.2 [95% CI: 1.2–13.9; P = 0.02] for pain at 6 and 12 months, respectively whereas the odds to develop pain at 12 months were 3.5 for ROCF recall (95% CI: 0.86–5.6; P = 0.04). Data were not significant for ROCF copy (P = 0.14 at 6 months; P = 0.09 for pain at 12 months) probably because the proportion of impaired patients was very low for this test.

**Predictors of the presence and severity of chronic postsurgical pain in each surgical group**

An additional series of logistic regression and linear regression analyses were performed in each surgical group, as a replication of the results obtained for the total sample of patients.

In each surgical group, increased TMT B time predicted both the presence of pain [odds ratio (OR): 1.07; 95% CI: 1.02–1.13; P = 0.009 in the arthroplasty group; OR: 1.07; 95% CI: 1.02–1.12; P = 0.005 in the breast group for pain at 6 months] and its severity (F = 5.86; P = 0.018 for pain at 6 months; F = 4.72; P = 0.034 for pain at 12 months in the arthroplasty group; F = 4.22; P = 0.04 for pain at 6 months in the breast group). Similarly decreased score on ROCF recall predicted both the presence of pain (OR: 0.83; 95% CI: 0.73–0.95; P = 0.006 in the arthroplasty group; OR: 0.91; 95% CI: 0.83–0.99; P = 0.04 in the breast group, for pain at 12 months) and its severity, although results were only close to significance in the breast group.

**Table 4** Logistic regression analysis (stepwise selection) for the identification of independent predictors for the presence of clinical meaningful chronic pain (average pain intensity ≥ 3/10) at 6 and 12 months in the total sample of patients

<table>
<thead>
<tr>
<th>Total sample of patients (breast, arthroplasty)</th>
<th>Odds ratioa</th>
<th>95% Confidence interval</th>
<th>P</th>
<th>Gammab</th>
<th>Somer’s Db</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months (n = 161)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spielberger state anxiety</td>
<td>1.01</td>
<td>1.00–1.02</td>
<td>0.015</td>
<td>0.560</td>
<td>0.559</td>
</tr>
<tr>
<td>TMT Bc</td>
<td>1.07</td>
<td>1.03–1.11</td>
<td>0.009</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ROCF-copyc</td>
<td>0.89</td>
<td>0.82–0.98</td>
<td>0.015</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical modeld</td>
<td>0.41</td>
<td>0.15–1.11</td>
<td>0.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 months (n = 148)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.95</td>
<td>0.91–1.00</td>
<td>0.06</td>
<td>0.633</td>
<td>0.33</td>
</tr>
<tr>
<td>Beck Depression Inventory</td>
<td>1.12</td>
<td>1.00–1.25</td>
<td>0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSQ passive coping</td>
<td>1.19</td>
<td>1.05–1.34</td>
<td>0.006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMT Bc</td>
<td>1.01</td>
<td>1.00–1.03</td>
<td>0.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ROCF copyf</td>
<td>0.86</td>
<td>0.77–0.96</td>
<td>0.023</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ROCF recallf</td>
<td>0.90</td>
<td>0.83–0.98</td>
<td>0.006</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The variables included in the model were those judged to be of clinical significance (age as a continuous variable, sex and the surgical model as dichotomous variables) and those distinguishing between painful and painless patients in both surgical groups at 6 or 12 months with a liberal significance level of P < 0.20 (TMT A, TMT B, ROCF copy, ROCF immediate recall, Spielberger state anxiety, Beck depression inventory, passive coping strategies of the Coping Strategies Questionnaire, as continuous variables). The same variables were selected for pain at 6 and 12 months. The order of presentation of variables in the final statistical model is that automatically generated by the computer.

Significant P-values are indicated in bold.

CSQ = Coping Strategies Questionnaire.

a Similar odds have been published in previous prospective studies aiming to find predictors for acute or chronic pain after surgery (Katz et al., 2005; Pinto et al., 2012).

b These coefficients (gamma, Somer’s D) measure the association between predicted and observed variables in the statistical model. They show that the model had a satisfactory predictive ability, particularly as these coefficients are of the same size as those obtained in previous studies in which they were judged clinically relevant (Wu et al., 2000).

c In these analyses, positive regression coefficients are observed for TMT B, in that the higher the time required to accomplish the task the greater risk for pain, while for ROCF conversely, negative regression coefficients are observed, in that the lower the score obtained the greater risk for pain.

d The lack of significant predictive value of the surgical model may be explained by the statistical model: the link of the surgical model with pain, although significant in univariate analyses (pain being significantly more prevalent in the arthroplasty group), may turn out to be non-significant in the final regression models. The main reason is that regression models depend on the predictors taken together, of their intercorrelations and of the stepwise procedure.
Table 5  Linear regression analyses (stepwise selection) for the identification of independent predictors for pain intensity at 6 and 12 months (based on the Brief Pain Inventory) in the total sample of patients undergoing total knee arthroplasty or breast cancer surgery

<table>
<thead>
<tr>
<th>Variables</th>
<th>b coefficient</th>
<th>Standard error</th>
<th>F</th>
<th>P</th>
<th>R² (a)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>6 months (n = 161)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beck Depression Inventory</td>
<td>0.072</td>
<td>0.040</td>
<td>3.51</td>
<td>0.06</td>
<td>0.2061</td>
</tr>
<tr>
<td>Spielberger state anxiety</td>
<td>0.029</td>
<td>0.011</td>
<td>8.60</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>TMT B</td>
<td>0.011</td>
<td>0.003</td>
<td>13.44</td>
<td>0.0003</td>
<td></td>
</tr>
<tr>
<td><strong>12 months (n = 148)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beck Depression Inventory</td>
<td>0.120</td>
<td>0.034</td>
<td>10.9</td>
<td>0.001</td>
<td>0.2123</td>
</tr>
<tr>
<td>TMT B</td>
<td>0.008</td>
<td>0.003</td>
<td>7.77</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>ROCF recall</td>
<td>-0.058</td>
<td>0.021</td>
<td>8.01</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>ROCF copy</td>
<td>-0.051</td>
<td>0.028</td>
<td>2.99</td>
<td>0.08</td>
<td></td>
</tr>
</tbody>
</table>

The variables included in the model were similar as those included in the logistic regression analyses (see Table 4): they included those judged to be of clinical significance (age as a continuous variable, sex and surgical model as dichotomous variables) and those distinguishing between painful and painless patients in both surgical groups at 6 or 12 months with a liberal significance level of $P < 0.20$ (TMT A, TMT B, ROCF-copy, ROCF-immediate Recall, Spielberger state anxiety, Beck Depression Inventory, passive coping strategies of the Coping Strategic Questionnaire, as continuous variables). The same variables were selected for pain at 6 and 12 months. The order of presentation of variables in the final statistical model is that automatically generated by the computer.

Significant $P$ values are indicated in bold.

Despite moderate values of $b$, suggesting modest effect sizes, the model has a satisfactory predictive ability because the squared multiple correlation ($R^2$) measuring the association between predicted and observed variables are of the same size as those obtained in previous similar studies in which results were judged clinically significant (Pan et al., 2006; Sullivan et al., 2011; Pinto et al., 2012).

In these analyses, positive regression coefficients are observed for TMT B, in that the higher the time required to accomplish the task the greater risk for pain, whereas for ROCF conversely, negative regression coefficients are observed, in that the lower the score obtained the greater risk for pain.

(F = 7.52; $P = 0.008$ in the arthroplasty group; $F = 3.2; P = 0.07$ in the breast group, for pain at 12 months). Decreased score on ROCF copy predicted the presence of pain in the breast group (OR: 0.87; 95% CI: 0.78–0.98; $P = 0.02$ for pain at 6 months; OR: 0.83; 95% CI: 0.73–0.95; $P = 0.006$ for pain at 12 months) and tended to predict pain severity at 12 months in the total knee arthroplasty group ($F = 3.2; P = 0.07$).

Thus results obtained for each surgical group as regards neuropsychological variables were similar to those of the total sample of patients, except for the lack of prediction of ROCF copy on the presence of pain in the arthroplasty group.

Results obtained for depression and anxiety were also similar in each group to those observed in the total sample of patients (not shown). Neither age nor preoperative pain (in the arthroplasty group), nor chemotherapy, radiotherapy or trait anxiety (in the breast group) significantly predicted the presence or intensity of chronic postoperative pain.

Predictors of neuropathic symptoms at 6 and 12 months

Several presurgical variables were weakly or moderately correlated with neuropathic symptoms (as assessed by the total DN4 score in patients with pain) at 6 months ($n = 52$) or 12 months ($n = 43$). These variables included ROCF-copy and recall scores...
(ROCF-copy: Rho: −0.19; P < 0.05 at 6 and 12 months; ROCF-recall: Rho: −0.14; P = 0.19 at 12 months), state anxiety (Rho: 0.20; P = 0.02 at 6 months; Rho: 0.15; P = 0.12 at 12 months) and depression (Rho: 0.19; P < 0.05 at 6 and 12 months). The variables included in the stepwise regression model were those judged to be of clinical significance (age as a continuous variable, sex and the surgical model as dichotomous variables) and those correlated with neuropathic symptoms at 6 or 12 months with a liberal significance level of P < 0.20 (e.g. ROCF-copy, ROCF recall, state anxiety, depression, as continuous variables). In these models, ROCF-copy and state anxiety were the only independent predictors of neuropathic symptoms at 6 months (F = 4.6; P = 0.03 for ROCF-copy; F = 4.4; P = 0.04 for state anxiety; F = 4.6; P = 0.03 for depression), whereas ROCF-copy and ROCF-immediate recall were the only independent predictors of neuropathic symptoms at 12 months (F = 5.3; P = 0.02 for ROCF-copy; F = 5.1; P = 0.03 for ROCF-immediate recall). Thus, poorer performances in the ROCF-copy and ROCF-immediate recall tests before surgery predicted significantly the number of neuropathic symptoms at 6 or 12 months in the sample of patients with pain.

Discussion

The aim of this prospective longitudinal 12-month study was to investigate the impact of attention, memory and executive function, measured by clinical tests, and their relationships to affective variables in determining the prevalence and severity of chronic pain and its neuropathic quality. We addressed this question, using two common conditions treated surgically, for which there is a risk of chronic postsurgical pain: total knee arthroplasty for osteoarthritis and breast surgery for cancer. These patients were representative of the population undergoing total arthroplasty for knee osteoarthritis and breast surgery for cancer (Poleschuk et al., 2006; Sullivan et al., 2011). We found that both neuropsychological measures of attention, visual memory and executive function and affective variables (state anxiety, passive coping strategies, depression) made an independent contribution to the prevalence and severity of chronic pain, as well as its neuropathic quality.

We chose to use highly sensitive neuropsychological tests, the TMT parts A and B, and the ROCF copy and immediate recall, which have been largely used for the assessment of cognitive function in patients with chronic pain (Lee et al., 2010; Moriarty et al., 2011; Kurita et al., 2012). We explored specifically the time (in seconds) to complete the TMT and did not analyse the error rates for this test because there were very few within patient variability for these values. We did not use ratio scores (e.g. TMT B/A or TMT B − A) in the lack of normative values and because of discrepant findings regarding their clinical use (Lezak, 1995; Martin et al., 2003; Oosterman et al., 2010b). Lastly we selected the immediate recall rather than the delayed condition of the ROCF, because we thought that the delayed condition would considerably increase the length and difficulty of testing without necessarily translating in better prediction of pain, as performances for immediate and delayed tests have been reported to be very close (Fastenau et al., 1999; Lezak, 2004).

Performance in the TMT A reflects visual search and motor speed only, whereas the TMT B requires the subject to maintain one set of information ‘on line’ while dealing with a second set of information and shifting attention back and forth between both sets (i.e. task or set shifting/switching) (Crowe, 1998; Korte et al., 2002; Sanchez Cubillo et al., 2009). The ROCF copy test assesses visuospatial, perceptive and constructional abilities, together with executive function (i.e. the strategies used by the subjects in the drawing of the complex figure, organization and mental planning) (Shin et al., 2006). Thus, the TMT B and the ROCF-copy tests, considered together, address cognitive flexibility, as this ability allows one to rapidly and efficiently adapt to different situations, which is an important component of executive function (Williams, 2010). However other neuropsychological tests, such as the Wisconsin Card Sorting Test or the Stroop Test, might also have been suitable to assess this cognitive function. Generally, cognitive flexibility spans a wide range of human abilities, including the likelihood of recognizing and adapting efficiently to various changing-task challenges (Leber et al., 2008; Kashdan and Rottenberg, 2010). Individual differences in cognitive flexibility have been associated with differences in reactivity to stressful situations (Williams, 2010). Comparison of the performances of our subjects to age and sex-adjusted normative values (Fastenau et al., 1999; Tomhaug, 2004) showed that most patients had normal values before surgery. However, arthroplasty patients performed less well in these tasks than breast surgery patients before surgery. This was probably because of their older age (Hedden and Gabrieli, 2004; Voineskos et al., 2012) and the presence of chronic pain. Indeed, neuropsychological performances were correlated with increasing age in our study, in line with previous reports (Tomhaug, 2004; Hester et al., 2005) and with chronic pain intensity, also consistent with previous findings (Moriarty et al., 2011; Oosterman et al., 2013). By contrast, performances in neuropsychological tests were not correlated with the analgesic or psychotropic medication received before surgery, apparently ruling out the possibility that the responses to these tests reflect cognitive deficit due to medication.

In our study, poorer results for the TMT part B and ROCF-copy tests were independently linked to chronic postsurgical pain in the total sample of patients in terms of prevalence or severity, as indicated by Tables 4 and 5, whereas the performances obtained on the TMT part A were not predictive. These results were particularly robust for the TMT B, which predicted both the presence and severity of pain at 6 and 12 months in the total sample of patients and in each surgical model. Conversely the ROCF copy seemed to be better predictive of pain in breast surgical patients, who were pain-free before surgery, than in arthroplasty patients, most of whom had presurgical pain. It is possible that some neuropsychological tests are more sensitive to predict ‘new’ pain generated by surgery than the continuation of preoperative pain. These data may suggest that patients with constitutively limited attentional resources or cognitive flexibility are at greater risk of suffering from chronic pain after surgery, independently of their affective status. Limited cognitive flexibility, as assessed by the TMT B and ROCF tests, may reflect individual premorbid variations of the corticolimbic circuitry (Miller and Cohen, 2001; Leber et al., 2008). Poor performance in the TMT B is, for
example, considered suggestive of frontal lobe damage (Demakis, 2004). Our data are consistent with observations of neuroplastic and brain morphology changes, particularly in the dorsolateral prefrontal cortex, in patients with chronic pain (Apkarian et al., 2004; Metz et al., 2009; Baliki et al., 2011, 2012; Mutso et al., 2012). Such individual differences in cognitive flexibility should perhaps be considered in relation to other individual differences, such as gene polymorphisms and personality traits (Williams, 2010). A deficit in cognitive flexibility could account for the inability to elaborate adaptive coping strategies or cognitive regulation of emotions to deal with chronic pain (Solberg et al., 2009). Thus several studies have highlighted the specific contribution of flexibility to maladaptive coping, such as catastrophizing, in patients with chronic pain (McCracken et al., 2007; Wicksell et al., 2010). Studies on coping have indicated that the crucial element in successful adaptation is not so much the particular strategies used, but rather whether the coping strategies are applied flexibly, in a manner corresponding to the nature of the stressor (Bonanno et al., 2004). Consistent with this notion, we found that passive coping, including pain catastrophizing, as assessed with the Coping Strategies Questionnaire, independently predicted chronic pain intensity at 12 months and was negatively correlated with TMT B score before surgery. These data may suggest that passive coping mediates the relationship between impaired neuropsychological functioning and chronic pain.

Another finding of our study was that poorer performances in the ROCF-immediate recall test, which assesses visual memory, was also independently associated with chronic pain prevalence and severity 12 months after surgery as indicated by Tables 4 and 5, with similar predictive values in each surgical model. The precise anatomical brain regions associated with performance in this test have yet to be determined, but poor performance may be associated with hippocampal dysfunction (Kraft et al., 2012). It has been shown in animal models and in patients with chronic widespread pain, that the hippocampus plays a fundamental role in pain perception (McEwen, 2001; Apkarian et al., 2009; Martuscello et al., 2012; Mutso et al., 2012). The hippocampus is connected to the parabrachial and thalamic regions through neuronal networks modulating spinal nociceptive processing through the activation of descending modulatory controls from the brainstem (Martuscello et al., 2012). It may, therefore, be a key structure involved in the relationships between pain and mood, coping strategies and memories about pain (Duric et al., 2006). This hypothesis is consistent with our findings that depressive symptoms, as assessed by the Beck Depression Inventory, also independently predicted chronic pain at 12 months in our patients.

The ROCF-copy and recall test results were also significantly linked with neuropathic symptoms (e.g. burning, tingling, electric shocks), as assessed with the validated DN4 questionnaire (Bouhassira et al., 2005), although the strength of such association was less robust, as neuropathic pain concerned a smaller sample of patients. Pain of a neuropathic nature seems to be most closely linked to variables assessing memory and cognitive flexibility. These results are consistent with those of clinical studies showing that morphometric abnormalities involving the prefrontal cortex are strongly related to pain characteristics, including the neuropathic nature of pain, in particular (Apkarian et al., 2009).

Furthermore, recent experimental data have indicated that hippocampus-mediated behaviour, synaptic plasticity and neurogenesis are abnormal in neuropathic rodents (Kodama et al., 2011; Mutso et al., 2012). Conversely, it has been shown that upregulation of cytokine tumor necrosis factor in the hippocampus, damping the hippocampal noradrenergic transmission involved in pain modulation, may induce behavioural pain symptoms in neuropathic animals (Martuscello et al., 2012). These data are consistent with recent findings showing that pain with neuropathic characteristics, as assessed with the DN4 questionnaire, induces a specific burden of illness in patients not found in patients with non-neuropathic pain, regardless of pain intensity or duration (Attal et al., 2011).

Another possibility to account for our results is that the cognitive performances obtained before surgery mainly reflect the anticipation of pain or surgery, particularly in patients with higher levels of anxiety, depression or maladaptive coping, and that this, in turn, predicts pain chronicity. This may be especially the case for breast surgery patients, who anticipate a stressful and potentially painful surgical procedure. A new neuropsychological evaluation after surgery might have contributed to rule out the effects of anticipation. This was not performed because of the difficulties to interpret postsurgical values: in fact, several patients had new or increased pain after surgery, which may impact cognition (Moriarty et al., 2011), and many patients with breast cancer received chemotherapy after surgery, which may particularly affect the cognitive domains evaluated by our tests (e.g. working memory, attentional processing or cognitive flexibility) (Kesler et al., 2013). The anticipation of a potentially painful event in healthy subjects has been reported to increase attention to pain and to interfere with the performance of tasks (Crombez et al., 1998; Van Damme et al., 2004; Brown and Jones, 2008). However, conflicting results have been reported (Van Ryckeghem et al., 2012) and it has been suggested that the interference of pain anticipation in task performance may be more limited in time than interference related to pain (Van Damme et al., 2002; Van Ryckeghem et al., 2012). In our study, neuropsychological tests were carried out 1 month before surgery, limiting the interference effect of anticipation. Furthermore, the two tests measuring attention and executive function—TMT B and ROCF-copy—were more consistent predictors of the presence or severity of chronic pain than measurements of pain coping or anxiety, and they predicted pain independently of these affective factors. We therefore believe that, although anticipation of pain or surgery could potentially have a deleterious impact on cognitive performance in our patients, it would not be sufficient, on its own, to account for these findings. It is more likely that both anticipation of pain or surgery and limited cognitive flexibility/attention might concur with the present results. Thus the effects of pain anticipation are probably enhanced particularly in patients with limited cognitive flexibility or memory.

Several potential limitations of our study should be outlined. First, reporting an association between scores in cognitive tests and self-reported measures of pain is not considered sufficient to establish causality (Hill, 1965). However, results of multivariate analyses confirmed those of univariate analyses and were observed in multiple tests; our study was prospective and a very large proportion of presurgical subjects were followed...
after a painful event. Chronic pain conditions or to limit the risk of pain chronicity able individuals should help to reduce the burden of pain in stressful situations in vulnerable individuals (Moriarty et al., 2011). However, patients with any evidence of cognitive deterioration were excluded from the study. Lastly, our statistical approach was exploratory and not confirmatory (Tabachnik and Fidell, 2007). Although we selected clinically relevant potential predictive variables, stepwise regression procedures have limitations (Derksen and Keselman, 1992) and therefore our results should be now confirmed by further statistical studies, using a confirmatory approach.

Our results have important clinical implications. They suggest, for the first time, that limited cognitive flexibility may be linked to the mechanisms of pain chronicity in patients (Solberg Nes et al., 2009). Although our data also suggest a relationship between impairment of cognition and neuropathic quality of pain, further explorations of other pain dimensions using techniques such as quantitative sensory testing would be helpful to determine whether these cognitive variables may also predict more specific components of pain such as allodynia, hyperalgesia or temporal summation. Our patients displayed no major clinical decline in cognitive functioning before surgery. Nevertheless, our findings suggest that patients with deficits of executive function or memory as a result of brain conditions, such as Parkinson’s disease, brain trauma, Alzheimer’s disease or mild cognitive impairment, would be at higher risk of developing chronic pain after a painful event, such as surgery. Interestingly it has recently been found that older adults reporting more severe pain intensity either at that moment or within the past 4 weeks have smaller hippocampal volumes than paired controls (Zimmerman et al., 2009). Our results also highlight the relevance of incorporating simple neuropsychological screening tests, such as the TMT B test, in future prognostic models for predicting the development of chronic pain (Hegarty and Shorten, 2012; Theunissen et al., 2012). Finally, they imply that focusing interventions on cognitive flexibility and emotion regulation in stressful situations in vulnerable individuals should help to reduce the burden of pain in chronic pain conditions or to limit the risk of pain chronicity after a painful event.

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