Exploratory Study

The Added Value of Sensitivity to Nonnoxious Stimuli to Predict an Individual's Sensitivity to Pain

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Background: Simple tools are needed to predict postoperative pain. Questionnaire-based tools such as the Pain Sensitivity Questionnaire (PSQ) are validated for this purpose, but prediction could be improved by incorporating other parameters.

Objectives: To explore the potency of sensitivity to nonpainful stimuli and biometric data to improve prediction of pain.

Study Design: Transversal exploratory study.

Setting: Single clinical investigation center.

Methods. Eighty-five healthy volunteers of both genders underwent a multimodal exploration including biometry, questionnaire-based assessment of anxiety, depression, pain catastrophizing, sensitivity to smell, and the PSQ, followed by a psychophysical assessment of unpleasantness thresholds for light and sound, and sensitivity to mechanical, heat, and cold pain. These last 3 parameters were used to calculate a composite pain score. After a multi-step selection, multivariable analyses identified the explanative factors of experimental pain sensitivity, by including biometric, questionnaire-based, and psychophysical nonnociceptive sensitivity parameters, with the aim of having each domain represented.

Results: Female gender predicted mechanical pain, a younger age and dark eyes predicted cold pain, and the PSQ predicted heat pain. Sensitivity to unpleasantness of sound predicted mechanical and heat pain, and sensitivity to unpleasantness of light predicted cold pain. Sensitivity to smell was unrelated. The predictors of the composite pain score were the PSQ, the light unpleasantness threshold, and an interaction between gender and eye color, the score being lower in light-eyed men and higher in all women. The final multivariable multi-domain model was more predictive of pain than the PSQ alone (R^2 = 0.301 vs 0.122, respectively).

Limitations: Sensitivity to smell was only assessed by a short questionnaire and could lack relevance. Healthy volunteers were unlikely to elicit psychological risk factors such as anxiety, depression, or catastrophizing. These results have not been validated in a clinical setting (e.g., perioperative).

Conclusion: The predictive potential of the PSQ can be improved by including information about gender, eye color, and light sensitivity. However, there is still a need for a technique suitable for routine clinical use to assess light sensitivity.

Key words: Personalized medicine, postoperative pain, senses, prediction, photophobia, hyperacusis, eye color, hypervigilance, sensory over-responsivity.

Trial Registration: These explorations were declared on ClinicalTrials.gov (NCT03113903) prior to starting this study.

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Predisposition to feel pain depends on innate and environmental mechanisms (1,2). Clinicians need simple tools to assess pain sensitivity, such as the Pain Sensitivity Questionnaire (PSQ) (3), which is able to predict pain after surgery (4), although its screening potency might be improved by including other predictors, such as female gender (5), and psychological factors such as anxiety (6-8), pain catastrophizing (7,9,10), fear (11), or hypervigilance (12,13). In line with this, screening pain sensitivity might be further improved by assessing responsiveness to innocuous stimuli (14-16). Furthermore, sensory over-responsivity (SOR) could signal altered sensory modulation, and has a relationship with pain sensitivity in healthy humans (17), and to hyperalgesia in chronic pain patients (18).

To enhance the screening potency of the PSQ, we studied the added value of a set of other biometric and nonnociceptive sensitivity factors, using data from a previous study conducted to validate the [German] version of the PSQ (19). In healthy volunteers, pain sensitivity was measured by psychophysical assessment; the parameters tested included biometry, anxiety, depression, pain catastrophizing, the PSQ, as well as nonnociceptive visual, hearing and olfactory sensitivity, by means of psychophysical measurements when possible, or a questionnaire otherwise. Because of reports of the influence of eye color (20) and ABO blood type (21) on pain sensitivity, this was also collected.

Methods

This study obtained ethical approval by the Comité de Protection des Personnes Ile-de-France I, was authorized by the French competent authority (ANSM), and registered on ClinicalTrials.gov (NCT03113903). All volunteers gave written informed consent. The methods for the main study have been previously detailed (19). Only that part of the main study conducted on 85 healthy volunteers (aged 18-60) was used in the analysis, as only they underwent a psychophysical assessment of pain sensitivity. The study design is summarized in Fig. 1. We noted the participant's age, gender, body mass index (BMI), ABO blood type when available, and eye color defined as "dark" if medium brown, dark-brown or black iris, and "light" otherwise (22). The volunteers answered the following questionnaires: the PSQ (3), the Pain Catastrophizing Scale (23), and the Hospital Anxiety & Depression Scale (24); all were used in their validated [French] version (19,25,26). In addition, we administered a short pilot questionnaire made of the 4 more relevant questions of the Odor Awareness Scale (27) (Table 1).

Psychophysical examination was conducted in order of growing discomfort. Sensitivity to sound and light were assessed successively in a room insulated from external sound and light. The procedure was explained to the volunteer before starting, in terms of the difference between uncomfortable (i.e., the lowest loudness/light level inducing any sort of discomfort) and intolerable. Sound sensitivity was determined by the standardized uncomfortable loudness level (ULL, in dB) (28). Pure tones were generated by an audiometer (MADSEN Orbiter 822, GN Otometrics, Taastrup, DK) and delivered through headphones. Testing was conducted successively for right, then left ear, at a low (500 Hz) then at a high (2000 Hz) frequency. The volunteer signaled uncomfortableness by raising a hand. The acoustic stimulations (short sounds lasting one second separated by one second of silence) started at 60 dB hL and were raised by 5 dB steps until ULL was reached. The maximum possible level to deliver was 110 dB hL, and was noted as the default ULL if uncomfortableness had not been reached. In case of uncertainty, the measurement was redone, with a maximum of 4 tests per ear and frequency. If the difference in ULL for the 2 ears did not exceed 20% of the mean, the final ULL value for each frequency (ULL500Hz and ULL2000Hz) was the average of both ears, or the lower of the 2 otherwise.

We assessed light sensitivity by applying light generated by a multi-LED studio photography lamp (Lykos Daylight®, Manfrotto, Cassola, Italy). We had previously determined the levels of intensity to administer (expressed as a percentage of the maximal intensity set by the manufacturer), and reliability was checked by a test-retest. We used dim background lighting (5 lux) in the room, with the ambient light source behind the volunteer, and the volunteer sitting facing the lamp, with eyes at a fixed distance of 180 cm from it. All tests were conducted by the same examiner, who covered the lamp with a large cardboard screen between each exposure, set the light intensity of the lamp, uncovered the lamp for one second for each exposure, then covered it again and asked the volunteer whether this was unpleasant. The exposure time was brief to avoid the volunteer to get used to the light because of pupil constriction. Light intensity was increased stepwise until the light unpleasantness threshold (LUT) was reached. Exposures were separated by a 20 second recovery period. As the thresholds observed in the pilot study displayed a log-normal distribution (29,30), we used a logarithmic scale with steps fixed at 4, 5, 7, 9, 12, 16,

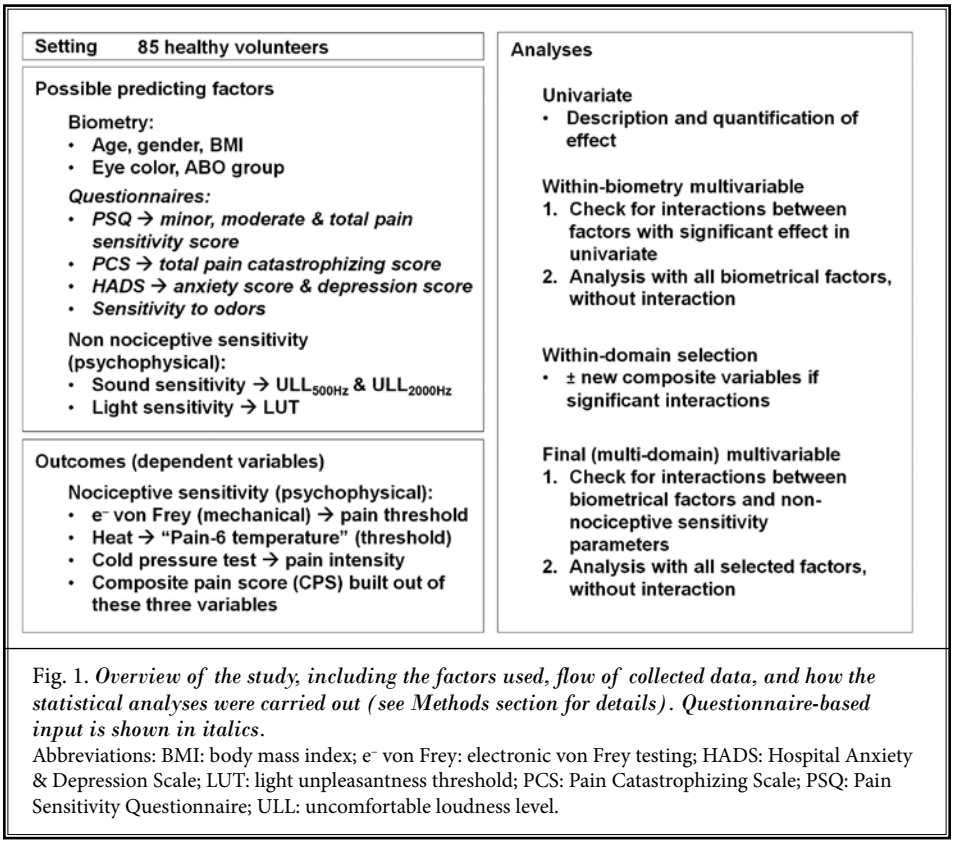

Fig. 1. *Overview of the study, including the factors used, flow of collected data, and how the statistical analyses were carried out (see Methods section for details). Questionnaire-based input is shown in italics.*
Abbreviations: BMI: body mass index; e⁻ von Frey: electronic von Frey testing; HADS: Hospital Anxiety & Depression Scale; LUT: light unpleasantness threshold; PCS: Pain Catastrophizing Scale; PSQ: Pain Sensitivity Questionnaire; ULL: uncomfortable loudness level.

21, 28, 37, 49, 65, 85, and 100% of the maximum possible intensity, which corresponded to 564 lux (meter-controlled). If unpleasantness had not been reached by this point, then the default LUT was noted as the 100% value.

The other psychophysical tests were conducted at a fixed room temperature of 24°C, on the side of the nondominant hand. Mechanical puncture pain thresholds were measured with an electronic von Frey device (Somedic, Hornby, Sweden), after a training session on the thenar eminence. Thresholds were measured 5 times on the volar face of the forearm, and these values were averaged. If the applied pressure reached 500 g, the test was stopped and this value was noted. Then, warm and heat pain thresholds (an average of 3 consecutive values) were measured using a PATHWAY (Medoc Ltd, Ramat Yishai, Israel) equipped with an ATS thermode, on the volar face of the forearm. Then, the "pain-6 temperature" was determined stepwise, as the temperature to induce pain rated as 6 on a numerical rating scale from 0 to 10 ("the worst pain imaginable"). Lastly, the volunteer underwent a cold pressure test (CPT), with a 2 minute immersion of the foot in a 4°C water bath. The volunteer continuously reported pain intensity on an electronic visual analog scale (0 to 10, as above). Pain intensity was averaged, either over the entire 2 minutes (representing tolerance to cold-induced pain), or for the first 30 seconds alone, the former representing tolerance to pain, and the latter sensitivity. In case of foot withdrawal before the end of the 2 minute exposure, the cursor was set at 10.

The study outcomes were the psychophysical parameters of pain sensitivity. Mechanical pain sensitivity was represented by the mechanical pain threshold. To represent the sensitivity to painful heat and painful cold, we chose the parameters which were best predicted by

Table 1. *Short questionnaire on sensitivity to odors.*

Question (short designation) [Rank in the original version]
Do you notice food odors emanating from houses when you are outdoors? ("outdoors") [3]
You are in a public space sitting close to someone who has an unpleasant smell. Do you look for another seat if possible? ("neighbor") [31]
Do you notice the smell of people's breath or sweat? ("breath-sweat") [8]
When you visit someone else's house, do you notice how it smells? ("indoors") [5]

The questions are presented here in the same order as in the questionnaire for the participants in the current study. The source for these questions (with their place in the original questionnaire) is: Smeets MA et al. The Odor Awareness Scale: a new scale for measuring positive and negative odor awareness. Chem Senses 2008;33:725-34. The answers to each question were marked on a 5-point Likert scale ("No, not at all"; "No, not particularly"; "Do not know / no opinion"; "Rather yes"; "Yes, completely"). For subsequent analysis, these answers were converted into ordinal numbers (–2, –1, 0, +1 and +2, respectively), and a composite score was created by averaging the values of the 4 questions. The responses expressed discomfort (i.e., either "Rather yes" or "Yes, completely") to the "breath-sweat", "indoors", "neighbor", and "outdoors" items, respectively in 77 (90.6%), 45 (52.9%), 71 (83.5%), and 62 (72.9%) of the cases. The respective calculated sub-scores (median and [1st and 3rd quartile]) were 1 [1 ; 2]; 1 [–1 ; 1]; 1 [1 ; 1]; and 1 [–1 ; 1] (i.e., the value '1' corresponds to the "Rather yes" response). The average score for the 4 items was 0.7 ± 0.6.

the PSQ, respectively the "Pain-6 temperature" and the averaged pain intensity within the first 30 seconds of immersion. In the main study to test the external validity of the [French] version of the PSQ (19), a trend was noted for each type of psychophysical pain perception; significance was not reached for all parameters. To improve statistical power and because pain involves various components of nociception, we determined a composite outcome to represent overall pain sensitivity. We used Silverman's integrated approach (31), by summing the standardized scores calculated for each of the 3 nociceptive components. For each individual and each component, a standardized subscore was calculated as: (ranked value within the sample) / ([mean theoretical rank] –1), with mean theoretical rank = (sample size +1) / 2. The rank was calculated in increasing order for the thresholds, and decreasing order for the pain intensity. Finally, a composite pain score (CPS) was calculated as the sum of these 3 sub-scores.

Data analysis was performed using Microsoft Office Excel 2010 (Redmond, WA) and XLStat (Addinsoft, Paris, France). Each variable was described and normality was checked. Numerical data were expressed by mean ± standard deviation in the case of a Gaussian distribution, and otherwise as quartiles. Nominal data were expressed by the number of cases and the percentage. We also stated that, in the case of nested variables, new composite variables could be built. This was a complete-case analysis with no missing data allowed (except for ABO blood type, for which an "unknown" modality was created). For inferential analyses, the significance threshold was set at 5%.

As inferential analyses were conducted on a group of 85 volunteers, whose size had been determined for other purposes, we aimed to reduce the number of variables to enter into the final pain sensitivity prediction models through a comprehensive stepwise selection. Ideally, the number of factors to be entered should not exceed 8, and should equally represent all these domains: biometric, psychometric, PSQ, and each nonnociceptive sensitivity. We used intermediate analyses to select the factors to enter into the final multidomain multivariable analyses. First, we tested the relationship of pain sensitivity with each potential predictor, using a simple linear regression for numerical variables, and an analysis of variance (ANOVA) for categorical variables. The strength of relationship was assessed for each factor by the β coefficient. In each domain where several variables were assessed (e.g., anxiety, depression, and pain catastrophizing for psychometry; the "minor," "moderate," and total score from the PSQ; ULL500Hz and ULL2000Hz for sound sensitivity), we selected the factor with the strongest relationship with the dependent variable. Intermediate analyses were conducted within the biometric domain to help selection and to avoid bias. Firstly, multicollinearity was checked by testing each parameter versus every other one, by the appropriate test (i.e., linear regression or between-groups comparison). In case of collinearity, we retained the factor with the best physiological relationship with pain sensitivity; we also considered any recruitment bias to explain such an effect.

Second, we conducted multivariable analyses on the dependent variable within the biometric domain: one set of analyses by inputting into the model only those factors which had a statistical relationship in the univariate analyses, with all the possible first-order interactions; and the other one by entering all the factors, without any interaction. This intermediate selection step was conducted because multicollinearity or interactions often involve biometric factors. For the multidomain multivariable analyses, we prioritized the factors found to be predictive in the previous analyses, but also wanted for each domain to be represented by at least one variable, the one with the best relationship with psychophysical pain sensitivity (even if non-significant). These final analyses were conducted by analyses of covariance with no selection process within the model. After checking the effect of interactions between each biometrical factor and each parameter of nonnociceptive sensitivity, the final models included all the parameters previously selected, and no interaction but those found to be predictive and relevant in the previous analyses. Multicollinearity was checked by the variance inflation factor (VIF), and model performance by the coefficient of determination (R^2).

Results

The characteristics of the 85 healthy volunteers were: age 32.2 years ± 11.3, Body Mass Index (BMI) 23.2 ± 3.0, 31 with dark eyes (36.5%), anxiety score 4.5 ± 2.4, depression score 1.5 ± 1.6, catastrophizing total score 11.6 ± 8.3, and total pain sensitivity score (PSQ) 4.1 ± 1.2. Their ABO blood type was: 36 A (42.4%), 32 O (37.6%), 2 AB (2.4%), and 15 unknown (17.6%). Forty-three were women (50.6%) and 42 were men (49.4%). The responses to the short questionnaire on sensitivity to odors are shown on Table 1.

There was a high multicollinearity within the psychometrical domain, within the 3 scores of the

PSQ, and between the 2 ULLs. Within the biometrical domain, BMI was lower in women than in men (P < 0.0001), and positively correlated with age (P = 0.025). Since we interpreted this as a recruitment bias, we prioritized gender or age to BMI in the final multivariable analyses, but BMI was still considered in the univariate, as well as in the within-biometry multivariable analyses, as a covariate. ULL500Hz and ULL2000Hz also correlated positively with age (P = 0.018 and P = 0.041, respectively), although they were lower in the women volunteers (P = 0.015 and P = 0.006, respectively), in accordance with the literature (32).

Table 2 shows the analyses of the mechanical pain threshold. The univariate analyses showed that the threshold was lower in women, and correlated positively with LUT and ULL500Hz and ULL2000Hz. After the selection process, being a woman and sound sensitivity (ULL2000Hz) predicted mechanical pain sensitivity.

Table 3 shows the analyses of the Pain-6 temperature (heat pain threshold), which had been log transformed because of a log-normal distribution. The univariate analyses showed that this threshold correlated negatively with the 3 scores of the PSQ, and correlated positively with the ULL500Hz and ULL2000Hz. After

Table 2. *Predictive analyses of the mechanical pain threshold.*

Factor	Univariate analysis		Multivariable analysis (biometry only) [a]		Selected? (reason)	Multivariable analysis (all domains) [b]	
	***P* value**	**β (95%CI)**	***P* value**	**β (95%CI)**		***P* value**	**β (95%CI)**
Women (vs men as ref.)	**0.001**	**–0.341 (–0.546, 0.135)**	**0.023**	**–0.296 (–0.549, 0.042)**	yes (1)	**0.014**	**–0.249 (–0.447, 0.051)**
Dark eyes (vs light as ref.)	0.298	–0.114 (–0.331, 0.103)	0.599	–0.057 (–0.272, 0.158)	no (1)		
A blood type (vs O as ref.)	0.919	–0.013 (–0.260, 0.235)	0.945	0.008 (–0.204, 0.240)	no (1)		
AB blood type (vs O as ref.)	0.943	–0.009 (–0.257, 0.239)	0.908	0.013 (–0.204, 0.229)			
Age	**0.019**	**0.253 (0.042, 0.464)**	**0.292**	0.125 (–0.110, 0.361)	yes (2)	**0.314**	**0.100 (–0.097, 0.298)**
BMI	**0.025**	**0.242 (0.031, 0.454)**	**0.747**	0.042 (–0.216, 0.299)	no (2)		
Anxiety	0.498	0.074 (–0.143, 0.292)			no (1)		
Depression	0.885	–0.016 (–0.234, 0.202)			no (1)		
Catastrophizing	0.341	–0.104 (–0.322, 0.113)			yes (3)	0.104	–0.156 (–0.345, 0.033)
PSQ (minor)	0.132	–0.165 (–0.380, 0.051)			no (1)		
PSQ (moderate)	0.300	–0.114 (–0.331, 0.103)			no (1)		
PSQ (total)	0.125	–0.168 (–0.383, 0.047)			yes (3)	0.592	–0.052 (–0.246, 0.141)
Odor sensitivity	0.294	0.115 (–0.102, 0.332)			yes (4)	0.197	0.124 (–0.066, 0.314)
LUT	**0.018**	**0.256 (0.045, 0.467)**			yes (5)	0.124	0.151 (–0.042, 0.344)
ULL500Hz	**0.001**	**0.351 (0.147, 0.556)**			no (3)		
ULL2000Hz	**< 0.0001**	**0.461 (0.267, 0.655)**			yes (6)	**0.003**	**0.323 (0.117, 0.530)**
For blood type, P = 0.993 for the whole model			P = 0.026 for the whole model (adjusted R^2 = 0.108)			P < 0.0001 for the whole model (adjusted R^2 = 0.277)	

When the tested factor is nominal, the data are given for the modalities tested vs. the modality taken as the reference class ("ref."). Each β coefficient (i.e., standardized) is shown with its 95% confidence interval (CI) limits. The higher the β value, the stronger the relationship; a significant relationship (shown in bold) is defined by a P value < 0.05 and the exclusion of the null value within the 95% CI limits. The reasons to select the factor were 1) effect in all previous analyses; 2) effect in univariate analysis only, but kept as covariate; 3) no effect in univariate analysis, but strongest effect within the domain; 4) no effect in univariate analysis, but sole factor within the domain; 5) effect in univariate analysis, and sole factor within the domain; 6) effect in univariate analysis, and strongest effect within the domain. The reasons not to select the factor were 1) no effect since univariate analysis; 2) collinear with age and gender; 3) effect in univariate analysis, but less effect within the domain. Notes: a: only the analysis of all factors without interaction is shown; the analysis of the factors found significant in the univariate analysis, plus the interactions between each other showed no significant interaction; b: only the analysis of all factors with no interaction is shown; the analysis of the factors plus the interactions between each biometric parameter and each parameter of nonnociceptive sensitivity showed no significant interaction.

Table 3. *Predictive analyses of the heat pain threshold ("Pain-6 temperature").*

Factor	Univariate analysis		Multivariable analysis (biometry only) [a]		Selected? (reason)	Multivariable analysis (all domains) [b]	
	***P* value**	**β (95%CI)**	***P* value**	**β (95%CI)**		***P* value**	**β (95%CI)**
Women (vs men as ref.)	0.093	–0.183 (–0.398, 0.031)	0.147	–0.194 (–0.459 0.070)	yes (1)	0.196	–0.131 (–0.330 ; 0.069)
Dark eyes (vs light as ref.)	0.117	–0.171 (–0.387, 0.044)	0.354	–0.105 (–0.330, 0.119)	no (1)		
A blood type (vs O as ref.)	0.052	–0.239 (–0.480, 0.002)	0.102	–0.201 (–0.443, 0.041)	no (1)		
AB blood type (vs O as ref.)	0.620	–0.060 (–0.301, 0.181)	0.644	–0.053 (–0.278, 0.173)			
Age	0.124	0.168 (–0.047, 0.383)	0.379	0.109 (–0.136, 0.354)	yes (1)	0.849	0.019 (–0.184, 0.223)
BMI	0.586	0.060 (–0.158, 0.278)	0.562	–0.078 (–0.347, 0.190)	no (1)		
Anxiety	0.187	0.144 (–0.072, 0.360)			yes (2)	0.488	0.069 (–0.128, 0.265)
Depression	0.863	–0.019 (–0.237, 0.199)			no (2)		
Catastrophizing	0.581	0.061 (–0.157, 0.279)			no (2)		
PSQ (minor)	< **0.0001**	**–0.415 (–0.614, –0.216)**			no (3)		
PSQ (moderate)	**0.0001**	**–0.402 (–0.602, –0.202)**			no (3)		
PSQ (total)	< **0.0001**	**–0.464 (–0.657, –0.270)**			yes (3)	**0.0001**	**–0.402 (–0.598, –0.205)**
Odor sensitivity	0.051	0.212 (–0.001, 0.425)			yes (4)	0.121	0.153 (–0.041, 0.346)
LUT	0.214	0.136 (–0.080, 0.353)			yes (4)	0.980	–0.003 (–0.199, 0.194)
ULL500Hz	**0.010**	**0.276 (0.067, 0.486)**			no (3)		
ULL2000Hz	**0.005**	**0.303 (0.095, 0.511)**			yes (3)	**0.047**	**0.213 (0.003, 0.423)**
For blood type, $P = 0.147$ for the whole model			$P = 0.344$ for the whole model (adjusted $R^2 = 0.174$)			$P < 0.0001$ for the whole model (adjusted $R^2 = 0.258$)	

In these analyses, the dependent variable (pain-6 temperature) has been log-transformed. When the tested factor is nominal, the data are given for the modalities tested versus the modality taken as the reference class ("ref."). Each β coefficient (i.e., standardized) is shown with its 95% confidence interval (CI) limits. The higher the absolute β value, the stronger the relationship; a significant relationship (shown in bold) is defined by a *P* value < 0.05 and the exclusion of the null value within the 95% CI limits. The reasons to select the factor were 1) no effect in univariate analysis, but kept as covariate; 2) no effect in univariate analysis, but strongest effect within the domain; 3) effect in univariate analysis, and strongest effect within the domain; 4) no effect in univariate analysis, but sole factor within the domain. The reasons not to select the factor were 1) collinear with age and gender; 2) no effect since univariate analysis; 3) effect in univariate analysis, but less effect within the domain. Notes: a: only the analysis of all factors with no interaction is shown; the analysis of the factors found significant in the univariate analysis, plus the interactions between each other showed no significant interaction; b: only the analysis of all factors with no interaction is shown; the analysis of the factors plus the interactions between each biometric parameter and each parameter of nonnociceptive sensitivity showed no significant interaction.

the selection process, the total score of PSQ and sound sensitivity (ULL2000Hz) predicted heat pain sensitivity.

Table 4 shows the analyses of pain intensity under the cold pressure test. The univariate analyses showed that pain intensity was higher in dark-eyed volunteers. It correlated negatively with age, positively with 2 of the 3 scores of the PSQ, and negatively with the LUT. After the selection process, eye color, age, and LUT predicted cold pain sensitivity.

As these values of R^2 in the final models for each component of pain sensitivity were similar, we did not use any weighting in the calculation of the CPS. The CPS displayed a Gaussian distribution ($P = 0.096$), with a mean value of 3.1 ± 1.3 for the whole sample set. Tables 5 and 6 show the results of the analyses of the CPS. The univariate analyses (Table 5) show that CPS was higher in women and in those with dark eyes. It correlated negatively with age, positively with the 3 scores of the PSQ, and negatively with the LUT, and the ULL500Hz and ULL2000Hz. The within-biometry multivariable analyses showed an effect of gender and age (when no interaction was tested), and an effect of eye color, age, and the interaction between gender and eye color. To better describe this interaction, a "gender / eye color" 4-class variable was created and its relationship with CPS was tested by a complementary one-way ANOVA. This model

Table 4. *Predictive analyses of the averaged pain intensity under cold pressure test.*

Factor	Univariate analysis		Multivariable analysis (biometry only) [a]		Selected? (reason)	Multivariable analysis (all domains) [b]	
	P value	β (95%CI)	*P* value	β (95%CI)		*P* value	β (95%CI)
Women (vs Men as ref.)	0.165	0.152 (–0.064, 0.368)	0.154	0.182 (–0.070, 0.433)	yes (1)	0.213	0.128 (–0.075, 0.332)
Dark eyes (vs light as ref.)	**0.004**	**0.309 (0.101, 0.517)**	**0.029**	**0.239 (0.026, 0.453)**	yes (2)	**0.047**	**0.200 (0.003, 0.396)**
A blood type (vs O as ref.)	0.640	0.058 (–0.187, 0.302)	0.826	–0.025 (–0.256, 0.205)	no (1)		
AB blood type (vs O as ref.)	0.246	–0.143 (–0.388, 0.101)	0.405	–0.090 (–0.305, 0.124)			
Age	**0.003**	**–0.318 (–0.525, –0.111)**	**0.022**	**–0.274 (–0.508, –0.041)**	yes (2)	**0.012**	**–0.265 (–0.470, –0.060)**
BMI	0.766	–0.033 (–0.251, 0.185)	0.195	0.168 (–0.088, 0.423)	no (1)		
Anxiety	0.397	–0.093 (–0.310, 0.124)			no (1)		
Depression	0.519	–0.071 (–0.289, 0.147)			no (1)		
Catastrophizing	0.211	0.137 (–0.079, 0.353)			yes (3)	0.072	0.176 (–0.016, 0.367)
PSQ (minor)	**0.012**	**0.272 (0.062, 0.482)**			yes (4)	0.067	0.181 (–0.013, 0.376)
PSQ (moderate)	0.091	0.185 (–0.030, 0.399)			no (1)		
PSQ (total)	**0.016**	**0.261 (0.050, 0.472)**			no (2)		
Odor sensitivity	0.492	–0.075 (–0.293, 0.142)			yes (5)	0.995	–0.001 (–0.193, 0.192)
LUT	**0.002**	**–0.331 (–0.537, –0.125)**			yes (6)	**0.007**	**–0.273 (–0.471, –0.076)**
ULL500Hz	0.559	–0.064 (–0.282, 0.154)			no (1)		
ULL2000Hz	0.421	–0.088 (–0.306, 0.129)			yes (3)	0.387	0.092 (–0.119, 0.303)
For blood type. $P = 0.403$ for the whole model			$P = 0.017$ for the whole model (adjusted $R^2 = 0.120$)			$P = 0.0002$ for the whole model (adjusted $R^2 = 0.250$)	

When the tested factor is nominal, the data are given for the modalities tested vs. the modality taken as the reference class ("ref."). Each β coefficient (i.e., standardized) is shown with its 95% confidence interval (CI) limits. The higher the absolute β value, the stronger the relationship; a significant relationship (shown in bold) is defined by a *P* value < 0.05 and the exclusion of the null value within the 95% CI limits. The reasons to select the factor were 1) no effect in previous analyses, but kept as covariate; 2) effect in all previous analyses; 3) no effect in univariate analysis, but strongest effect within the domain; 4) effect in univariate analysis, and strongest effect within the domain; 5) no effect in univariate analysis, but sole factor within the domain; 6) effect in univariate analysis and sole factor within the domain. The reasons not to select the factor were 1) no effect since univariate analysis; 2) effect in univariate analysis, but less effect within the domain. Notes: a: only the analysis of all factors with no interaction is shown; the analysis of the factors found significant in the univariate analysis, plus the interactions between each other showed no significant interaction; b: only the analysis of all factors with no interaction is shown; the analysis of the factors plus the interactions between each biometric parameter and each parameter of nonnociceptive sensitivity showed no significant interaction.

was also predictive ($P = 0.004$, adjusted $R^2 = 0.121$), CPS being lower (Tukey post hoc test) in light-eyed men (2.3 ± 1.2) than in light- and dark-eyed women (respectively 3.4 ± 1.2 and 3.6 ± 1.4); the dark-eyed men's subgroup (3.3 ± 1.1) was not different from either of these 2 clusters. After the selection process, multidomain multivariable analyses were conducted. The analysis of the factors plus the interactions between each biometric parameter and each parameter of nonnociceptive sensitivity, showed no significant interaction. In the final model (Table 6), the interaction between gender and eye color, subjective pain sensitivity (total score of PSQ), and LUT predicted CPS ($P < 0.0001$ for the whole model; adjusted $R^2 = 0.349$).

In all our multivariable analyses which did not test interactions, there was no relevant multicollinearity, apart from for BMI, with all VIFs being under 1.6. All these models improved the predictive power of the PSQ, as R^2 was 0.122 for the univariate analysis of CPS against PSQ-total (ANOVA). A synthesis of our results is shown in Fig. 2.

Discussion

Our results show that the predicting potency of PSQ could be sensibly improved by biometric factors and by parameters of nonnociceptive sensitivity. Nevertheless, it is not yet possible to interpret the discrepan-

Table 5. *Predictive analyses of the composite pain score (selection process).*

Factor or interaction	Univariate analysis		Multivariable analysis (biometry only)				Selected? (reason)
			All factors, no interaction		Factors with statistical effect in univariate, plus interactions		
	P value	β (95%CI)	*P* value	β (95%CI)	*P* value	β (95%CI)	
Women (vs men as ref.)	**0.006**	**0.298 (0.090, 0.507)**	**0.020**	**0.298 (0.048, 0.547)**	0.156	0.478 (–0.186, 1.142)	yes (1)
Dark eyes (vs light as ref.)	**0.026**	**0.241 (0.029, 0.453)**	0.152	0.154 (–0.058, 0.366)	**0.014**	**0.929 (0.193, 1.665)**	yes (1)
A blood type (vs O as ref.)	0.316	0.124 (–0.121, 0.369)	0.606	0.059 (–0.169, 0.288)			no (1)
AB blood type (vs O as ref.)	0.682	–0.050 (–0.296, 0.195)	0.729	–0.037 (–0.251, 0.176)			
Age	**0.002**	**–0.325 (–0.532, –0.119)**	**0.048**	**–0.234 (–0.466, –0.002)**	0.378	–0.129 (–0.420, 0.161)	yes (1)
BMI	0.165	–0.152 (–0.368, 0.064)	0.486	0.089 (–0.165, 0.343)			no (1)
Women* dark eyes [a]					**0.042**	**–0.366 (–0.720, –0.013)**	yes (1)
Women* age [b]					0.712	–0.114 (–0.730, 0.501)	no (2)
Dark eyes* age [c]					0.087	–0.557 (–1.196 ; 0.083)	no (2)
Anxiety	0.175	–0.148 (–0.364, 0.068)					yes (2)
Depression	0.795	–0.029 (–0.247, 0.190)					no (1)
Catastrophizing	0.560	0.064 (–0.154, 0.282)					no (1)
PSQ (minor)	**0.002**	**0.324 (0.117, 0.530)**					no (3)
PSQ (moderate)	**0.010**	**0.276 (0.066, 0.486)**					no (3)
PSQ (total)	**0.001**	**0.350 (0.145, 0.554)**					yes (3)
Odor sensitivity	0.084	–0.188 (–0.403, 0.026)					yes (4)
LUT	**0.006**	**–0.296 (–0.504, –0.087)**					yes (5)
ULL500Hz	**0.002**	**–0.327 (–0.533, –0.120)**					no (3)
ULL2000Hz	**0.0003**	**–0.382 (–0.583, –0.180)**					yes (3)
For blood type. $P = 0.506$ for the whole model			$P = 0.011$ for the whole model (adjusted $R^2 = 0.133$)		$P = 0.001$ for the whole model (adjusted $R^2 = 0.189$)		

The composite pain score (CPS) expresses the 3 components of nociception, i.e., mechanical and heat pain thresholds and cold pain intensity, with a similar weighting (see Methods for details). In this table, only the analyses conducted for the selection of factors to be entered into the final (multidomain) multivariable analyses, are shown. When the tested factor is nominal, the data are given for the modalities tested versus the modality taken as the reference class. Each β coefficient (i.e., standardized) is shown with its 95% confidence interval (CI) limits. The higher the absolute β value, the stronger the relationship; a significant relationship (shown in bold) is defined by a P value < 0.05 and the exclusion of the null value within the 95% CI limits. The reasons to select the factor were 1): effect in previous analyses; 2) no effect in univariate analysis, but strongest effect within the domain; 3) effect in univariate analysis, and strongest effect within the domain; 4) no effect in univariate analysis, but sole factor within the domain; 5) effect in univariate analysis and sole factor within the domain. The reasons not to select the factor were 1) no effect since univariate analysis; 2) no effect in multivariate analysis; 3) effect in univariate analysis, but less effect within the domain. Notes: a: data are given for the dark-eyed female class, versus the 3 other as reference classes; b: men is the reference class; c: light eyes is the reference class.

cies between the different factors in their abilities to predict each aspect of pain sensitivity, which could also be explained by underlying mechanisms (e.g., afferent fibers or central treatment).

Our results fit to the theory of SOR (14,33), while mechanisms linked to both hyperalgesia and SOR are involved in various chronic pain syndromes (18,34-37). To screen SOR in individuals, an Israeli team developed a Sensory Responsiveness Questionnaire (SRQ) (15), and showed that SOR in those who are healthy was associated with a greater sensitivity to painful stimuli (17); however, SOR did not influence the response to conditioned pain modulation (CPM), an indicator of inhibitory controls of pain (38). This suggests that this shared over-responsivity to noxious and nonnoxious stimuli could occur either on transmission, or during cortical

treatment of the input. It must be added that the cortical "pain matrix" largely overlaps with areas receiving nonnociceptive stimuli (39). Although this overlap may explain interactions between the different types of sensitivity (40), it could also signal a simple convergence towards common areas, in which any hypersensitivity could affect all these different aspects. Finally, our negative results on sensitivity to odors may challenge this SOR theory, but they can also be explained by a low sensitivity of the questionnaire-based assessment tool.

Contrary to the common belief that light-eyed people are more sensitive to light, over-sensitivity of dark-eyed people to pain had already been noted in studies of dental (41) and labor pain (20). This relationship was also reported in those who are healthy submitted to CPT, but was no longer found with a weaker noxious stimulation (42,43). Genetic underlying mechanisms must also be addressed, although eye color is polygenic. The genes that are most influential in creating darker eyes are *OCA2* (which regulates the synthesis of melanin) and *HERC2* (which regulates the occurrence of *OCA2*, a specific mutation strongly linked to blue eyes). There is no report of a direct association between any of these genes and pain. However, disorders affecting the chromosome region in which both genes are located are characterized by a higher sensitivity to pain or heat (44,45). On the other hand, *MC1R* is thought to influence pain sensitivity (46), but has less influence on eye color.

Over-sensitivity of women to pain is widely documented, but the broad scope of its mechanisms goes beyond the sole field of genetics (5). Our results confirm this trend, with a mean CPS of 3.7 in women vs 2.4 in men. More surprising was the interaction between gender and eye color, with a clear resistance to pain in light-eyed men. Although such results in a small and healthy sample must be interpreted cautiously, they can be summarized as an eye color effect limited to men, while the effect of women enhancing pain sensitivity seemed to override eye color. In a mechanistic approach, the cause of this interaction should be studied further, but not only in the field of gene-gene interactions. For example, interactions be-

Table 6. *Final multi-domain multivariable analysis of the composite pain score.*

Factor or interaction	*P* value	β (95%CI)
Age	0.107	–0.159 (–0.353, 0.035)
Dark-eyed women [a]	**0.017**	**0.256 (0.047, 0.465)**
Dark-eyed men [a]	**0.013**	**0.257 (0.055, 0.459)**
Light-eyed women [a]	**0.005**	**0.316 (0.098, 0.534)**
Anxiety	0.657	–0.042 (–0.232, 0.147)
PSQ (total)	**0.006**	**0.262 (0.077, 0.448)**
Odor sensitivity	0.282	–0.100 (–0.284, 0.084)
LUT	**0.033**	**–0.206 (–0.394, –0.017)**
ULL2000Hz	0.084	–0.178 (–0.381, 0.025)

The composite pain score (CPS) expresses the 3 components of nociception, i.e., mechanical and heat pain thresholds and cold pain intensity, with a similar weighting (see Methods for details). When the tested factor is nominal, the data are given for the modalities tested vs. the modality taken as the reference class. A new nested variable has been created to explore the interaction between gender and eye color. Each β coefficient (i.e., standardized) is shown with its 95% confidence interval (CI) limits. The higher the absolute β value, the stronger the relationship; a significant relationship (shown in bold) is defined by a *P* value < 0.05 and the exclusion of the null value within the 95% CI limits. Notes: a: versus light-eyed men is the reference class.

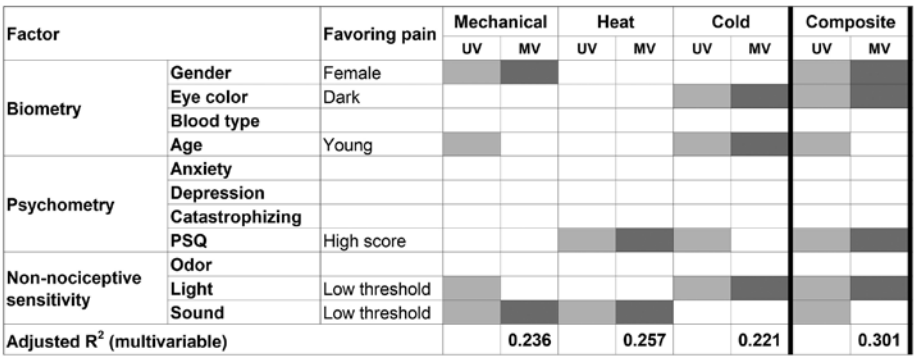

Fig. 2. *Synopsis of our results. Grey-shaded cells indicate a significant relationship between the factors (rows) and the different aspects of psychophysical pain sensitivity (columns). Relationships in multivariable analyses are signaled with a darker grey than in the univariate, due to the higher level of evidence. The composite pain sensitivity was assessed by the composite pain score (CPS) (see Methods section for details). The body mass index as a factor is not shown, as it was collinear with age and gender. R^2 is the adjusted coefficient of determination for the multivariable analysis, this when only the identified predictors were retained in the model. Abbreviations; UV: univariate analysis; MV: final multi-domain multivariable analysis.*

tween sex hormones and eye color may occur at the prenatal stage of development (47).

Despite our negative results, the ABO blood type, easy to collect in current care, should not be ignored, as pain sensitivity might be higher in AB types and lower in B types (21), while these types were almost absent in our sample. This is also true for psychometrical outcomes, which were not retained by our statistical models, mainly because over-anxious subjects had been discarded from our cohort of healthy volunteers for ethical reasons (19).

Another limitation is that only healthy volunteers were fully explored in this sub-study of the PSQ, while our observations should be validated in the clinical context, especially the perioperative one. For example, a study in patients undergoing breast cancer surgery tested multiple preoperative parameters, including PSQ, trait and state anxiety, depression, pain expectation, noxious liminal and supraliminal testing, and CPM (4); relevant postoperative pain was predicted by the PSQ, anxiety, younger age, and the type of procedure. Further validation should cover a wide range of surgical interventions, with the added difficulty of warranting an optimal pain relief.

A last point is how to easily assess nonnociceptive sensitivity during clinical routines. One option would be to develop simple portable devices to carry out a psychophysical assessment; another would be to collect questionnaire-based surrogates. For example, the SRQ addresses a wide panel of stimuli (15), but in the above-mentioned validation study, statistical power was improved by discarding those who were healthy with intermediate responses to the SRQ (17). Questionnaires have been developed to assess sensitivity to sound (48,49), and light (30,50). Those for light have been successfully validated against psychophysical thresholds; such tools should also be tested for pain sensitivity. There is, however, some uncertainty about their reliability, as sensitivity to unpleasantness of nonnociceptive stimuli might derive from various sources – each with its own level of treatment in the nervous system – and it is not yet known where SOR lies within this complex system. For example, in the sound domain, hyperacusis is independent of the context and is related to the auditory pathway, misophonia is contextual and follows supraspinal association processes, while phonophobia is related to fear of damage and lies within the domain of belief (32).

To conclude, we have confirmed the multifactorial aspect of pain sensitivity. While most of the factors we identified as favoring experimental pain sensitivity are easy-to-collect parameters (because they are biometric or questionnaire-based), we still need easy tools to assess sensitivity to nonnoxious stimuli. To make sure that they can be routinely used, such tools would also need to be highly affordable.

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