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INVESTIGATIVE REPORT

Validation of a Model of Itch Induction for Brain Positron Emission Tomography Studies Using Histamine Iontophoresis

Laure BERGERET[1,2], David BLACK[3] Jennifer THEUNIS[3], Laurent MISERY[4], Nicolas CHAUVEAU[1,2], Florent AUBRY[1,2], Hélène GROS[1,2], Gérard VIALLARD[1,2] and Pierre CELSIS[1,2]

[1]INSERM, Imagerie Cérébrale et Handicaps Neurologiques UMR 825, CHU Purpan, [2]Université de Toulouse Paul Sabatier, Imagerie Cérébrale et Handicaps Neurologiques UMR 825; CHU Purpan, Toulouse, [3]Skin Research Centre, Pierre Fabre Dermocosmétique, Toulouse and [4]Department of Dermatology, University of Western Brittany, Brest, France

Skin-brain signalling in itch reactions has been demonstrated with neuroimaging techniques showing specific brain activation. With positron emission tomography (PET), the itch model used must be adapted to technical and practical constraints. The technique of itch induction by histamine iontophoresis enables modulation of the sensation via the electrical charge applied. This itch model was validated on normal forearm skin of 56 subjects, with itch visual analogue scores peaking to approximately 1.0 cm after 3–4 min, falling to 0.2 cm at 15 min, with no influence of sex, zone, or order. Subsequently, the model was used in a PET study on 14 male volunteers, comparing histamine with physiological saline (control). The results show that the brain is able to discriminate these two conditions, with activated areas similar to those described previously, with, in addition, the anterior cingulate cortex and the insula being positively correlated with the intensity of the sensation. *Key words: itch; histamine; iontophoresis; brain activation*.

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David Black, CRP PFDC Hotel Dieu St Jacques, 2 rue Viguerie, FR-31025 Toulouse, France. E-mail: david.black@pierre-fabre.com

Itch is defined as an unpleasant sensation leading to the desire to scratch. The pathophysiology of itch remains complex. There are many techniques and mediators that have been used to induce itch experimentally.

After the prick test, histamine iontophoresis has become a widely used technique for the study of itch and the accompanying cutaneous axon reflex reaction of wheal and flare. It is defined as the application of an electrical potential that maintains a constant electric current across the skin and enhances the delivery of ionized as well as unionized moieties. Furthermore, it has been used as a model for itch induction in brain imaging studies (1–4), with the advantage over the prick test of being non-invasive, preserving the skin barrier, and producing a pure itch sensation. Some minor tingling sensations may be felt during current delivery, but this stops when the stimulation is switched off. Using iontophoresis, the characteristics of the itch sensation can be modulated by changing the stimulation parameters; for example, increasing the intensity of itch by increasing the electrical current used, or more precisely the current charge (5, 6), defined by Coulomb's law as: Q (current charge, mC) = I (current, mA) × t (time, s). Thus iontophoresis stimulation parameters used vary between studies, with varying consequences on the intensity of itch sensations evoked. For behavioural studies the duration and intensity of the induced itch is not of prime importance, but for brain imaging studies, the itch characteristics must be compatible with the constraints of the neuroimaging technique used.

With regard to positron emission tomography (PET), using $H_2{}^{15}O$ as the blood flow tracer, the main constraints are: (*i*) the time for image capture (2 min), (*ii*) the minimum time between two image capture sequences or runs (approximately 8 min in duration) to allow for elimination of radioactivity, and (*iii*) the skin site of stimulation being confined to the free non-catheterized arm. The first constraint requires that the time-course of the histamine-induced itch intensity is sufficiently characterized in order to predict the time of peak itch intensity. Knowing the onset time for peak itch will thus determine the moment at which the 2-min PET capture sequence is started in relation to the time of histamine application. Where the second constraint primarily concerns the safety of the patient, it must also be taken into account when planning experiments of this kind where several runs are made in order to improve the signal-to-noise ratio, thus improving the quality of PET images. However, a compromise has to be reached between the number of runs and the length of time spent by the patient immobilized in the PET scanner. Thus the itch stimulus needs to be repeated accordingly, requiring different skin sites to be used each time, with ideally a sufficiently strong but short-lived itch reaction. The model of choice for this induction tends towards the histamine iontophoresis model rather than that of the prick test, due to the latter having a greater itch intensity lasting for up to 20 min (7).

This brings us to the third constraint where it is important to verify that the site and order of stimulation

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does not influence the intensity of the itch sensation. The same site of the flexor forearm was used throughout the study, this being easily accessible and a routine site for skin testing in our laboratories. Although Magerl et al. (6) showed that itching scores showed no significant differences between body areas, the forearm seemed to give higher itch scores with the visual analogue scale (VAS) method. With the PET scan technique, one arm is catheterized for injecting the radiotracer ($H_2{}^{15}O$), leaving only one arm free for histamine stimulation. Thus, any possible bias due to a right–left influence on the intensity of itch must be checked.

The purpose of the present study was to validate the stimulation parameters of our histamine iontophoresis model for itch induction consistent with PET-$H_2{}^{15}O$ requirements. To accomplish this, two experiments were carried out. Firstly the variability of the itch sensation induced by multiple applications to different forearm sites was investigated. In practice, this involved analysing variation with sex, site and order. The data used for these analyses consisted of the intensity of perceived sensation over time (maximum intensity, duration). Secondly, the itch model was used in a PET study of brain activation in order to verify the areas normally involved in the itch sensation.

METHODS

Itch induction using histamine iontophoresis

The iontophoresis apparatus used consisted of an isolated constant current high voltage (HV) stimulator DS7A and trigger generator DG2A for biomedical use (Digitimer Ltd, Hertfordshire, UK). The former was used to set the current intensity (0.24 mA), pulse length (2000 μs), and voltage (300 V), whereas the latter was used to determine the total duration of pulse trains delivered (2 × 8 s), their latency of application (0 s), and frequency (900 Hz).

The anode consisted of a 12 mm diameter Finn chamber (Epitest Oy, Tuusula, Finland) connected to the trigger generator using 2 mm diameter wrapping wire inserted between the aluminium Finn chamber and adhesive tape. A 10 mm diameter filter paper disc was placed in the Finn chamber and 50 μl 1% histamine chloride (Stallergenes, Fresnes, France) was applied. This is the concentration frequently reported in previous studies (6–11). On top of this, a double-sided ring adhesive was attached (32 mm external diameter, 11 mm internal) which helped to maintain the histamine-soaked disc on the skin. The cathode consisted of an adhesive gel electrode, 22 × 34 mm (Type RT34, Skintact, Innsbruck, Austria), attached 10 cm distally to the anode (Fig. 1).

The ability of the iontophoresis technique to draw molecules into the skin depends on the current charge. The electrical current setting was 0.24 mA for a 16 s duration. With this configuration, the total charge is $Q = 0.24 \times 16 = 3.84$ mC, and current density $D = 0.25$ mA/cm^2 (electrode area = 0.95 cm^2).

Validation study

The study was approved by the local biomedical research ethics committee, and involved 56 healthy volunteers, (28 men, mean age 26.6 years and 28 women, mean age 25.1 years) who had given their written informed consent. Volunteer subjects were included with a phototype of III or less, according to the numerical classification of the colour of skin (from I to VI) developed by Fitzpatrick (12). In addition, all subjects were required to cease applying any skincare or cosmetic product on the forearm one week prior to the start of the study. Exclusion criteria were the following: those subjects with any history of allergy, atopic eczema, or other dermatological diseases, medication likely to interfere with the study (anti-histamines, corticosteroids or psychotropic drugs), and previous history of psychiatric or neurological disorders.

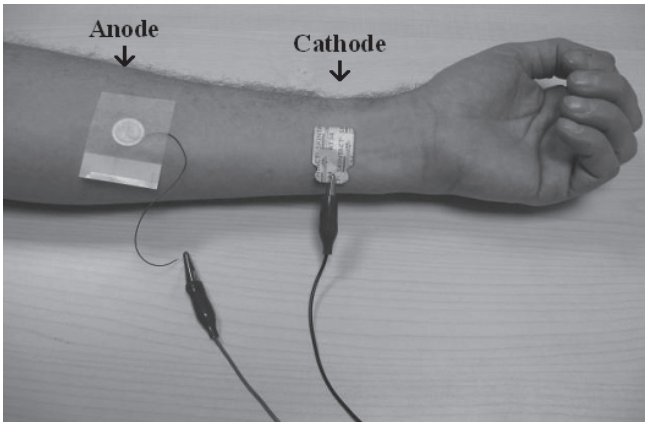

Fig. 1. Histamine iontophoresis electrodes in place on the flexor forearm.

Volunteers were requested to wash the skin on the forearm the evening before the test with no subsequent application of any creams or other cosmetic products. On the day of the test, the subject remained for at least 15 min in an air-conditioned room with the forearm exposed. Ambient conditions were measured and fell within the following ranges: temperature 20 ± 2°C, 45 ± 10% room humidity. The flexor aspect of each forearm was divided into two zones, with zones 1 and 2 corresponding to the right forearm and zones 3 and zone 4 to the left forearm. Histamine stimulations were carried out on each zone, with the order of testing being randomized. Following stimulation, the iontophoresis electrodes were removed and the itch intensity evaluated after 1, 2, 3, 4, 6, 8 and 15 min, this being the maximum length of time desired for these evaluations due to the constraints imposed by the PET scan. Itch was evaluated using the 10 cm VAS, where 0 = no itch, and 10 = worst possible itch experienced. This was also done before stimulation to check for zero itch. During this time, volunteers were not allowed to relieve their itch by scratching.

Statistical analysis

Statistical analysis of results was performed using the Statistica software version 6.1. Since sex may be a factor in the degree of wheal and flare induced by histamine (6), this was taken into account by the statistical analysis. In addition, the factors of zone (1, 2, 3, 4) and rank of stimulation (1st, 2nd, 3rd, 4th) were also included in the analysis involving a repeated measurement analysis of variance (ANOVA) ($p < 0.05$). Significant results were analysed *post hoc* using the Bonferroni test. Before stimulation (T0) the itch intensity was evaluated. Because subjects felt no itch sensation, this measure was not included in the statistical analysis.

PET brain activation study

The study was approved by the local biomedical research ethics committee, and involved a total of 14 healthy male volunteers

who were included after having given their written informed consent. They were selected from among the 28 volunteers who participated in the previous validation study as those having the greatest itch response to histamine.

Prior to inclusion, the subjects were re-tested for their reaction to the histamine stimulus in addition to an extra test involving physiological saline as a control. Subjects who responded positively to the former (VAS≥1), and negatively (VAS=0), to the latter were included. The other non-inclusion criteria were the same as the previous study.

$H_2{}^{15}O$ PET scans were taken during the application of two types of stimuli to the un-catheterized right forearm. Each type of stimulus was repeated three times in a blind randomized fashion. After each scan, the subject verbally rated the intensity of itch using the same numerical scale (NS) as that used for the visual analogue approach, with 0=no itch, 10=worst possible itch. The following PET scan was not started until the itch sensation had abated.

Histamine was applied as the test stimuli (H) using the iontophoresis set-up as previously described, with physiological saline also being applied iontophoretically as a control. The parameters of stimulation were the same as previously described. After the subject had been catheterized and was in position for the PET scans, the PET/stimuli sequence was started as follows: 0 min, apply stimulus for 16 s then remove electrodes; 2.5 min, start PET scan; 4.5 min, end PET scan and rate itch; 10–15 min, check for zero itch before starting next scan.

The head was immobilized and head position was aligned transaxially to the orbitomeatal line with a laser beam and controlled before each acquisition. Measurements of regional distribution of radioactivity were made with an ECAT HR (Siemens) PET camera with full-volume acquisition (planes, 63; thickness, 2.4 mm, axial field-of-view, 158 mm; resolution 4.2 mm in all directions). The duration of each scan was 120 s; approximately 6 mCi of $H_2{}^{15}O$ was administered.

PET data processing and analysis

Pre-processing and statistical analysis of the PET data was conducted using the Statistical Parametric Mapping 5 software (SPM5 revision 1782; The Wellcome Trust Centre for Neuroimaging, London, UK; www.fil.ion.ucl.ac.uk/spm). Images were realigned and co-registered with the mean image calculated from the whole set of PET images. They were then transformed into the standard space of the Montreal Neurological Institute PET template, and finally, smoothed with an 8-mm Gaussian filter. Images from all subjects were scaled to an overall cerebral blood flow (CBF) grand mean of 50 ml 100 $g^{-1}min^{-1}$. Data were analysed in two ways: (*i*) to reveal the brain regions activated relative to the histamine stimulus, regional cerebral blood flow (rCBF) images taken during histamine stimulation were compared with those taken with the control stimulus. To obtain an average activation map for all subjects, the functional data was combined in a "random-effects" analysis to identify these brain areas. A random-effects model takes into account between-subject variability and allows more generalized inferences from the data than a fixed-effects analysis. (*ii*) To assess associations of rCBF increase with the registered subjective variables, correlation analysis was performed. For this purpose, the recorded variables (itch rating) were integrated into the SPM analysis as covariates of interest. The difference in the VAS score for itching between the histamine and the saline stimulus condition was used for the correlation analysis. Resulting activation foci were regarded as significant if they survived a threshold of uncorrected $p<0.001$. Anatomical localization of activated brain regions was determined using the Montreal Neurological Institute Space Utility of SPM.

Statistical analyses of behavioural results

Statistical analysis of the score of subject's itch intensity was carried out with Statistica software, version 6.1. Differences between histamine and saline stimuli ratings were analysed with a repeated measurement ANOVA as previously, to check for condition effects (histamine vs. saline). This was also performed for rank effects only relative to each histamine and saline stimulus.

RESULTS

Validation study

The data are summarized in Fig. 2, showing the mean itch intensity scores for all four zones for men and women. The overall pattern was of an increase in itch scores in the first minute, reaching a maximum between 3–4 min, with a steady decrease thereafter, reaching near-zero values at 15 min. Table I provides further detail of itch scores in relation to the zone and the order of stimulation. In this case, only data from the 1st and 15th min, and the maximum score reported, have been presented for reasons of simplicity. These are also the three principal points that best represent the time-course of the itch intensity ratings. The mean maximum scores in Table I are the highest scores encountered per zone, per subject over the entire 15 min period. They are greater than the peak values in the graph, since the latter are means calculated for each time-point for all four zones, thus including a wider range of values.

Statistical analyses of variance revealed significant time-dependent differences for both men and women, with specific differences being found between certain time-points using the Fisher *post hoc* test. These can generally be summarized by the presence of a plateau of maximum intensity 2–4 min after stimulation in men, and 3–6 min after stimulation in women, both of which were significantly different from all other time-points,

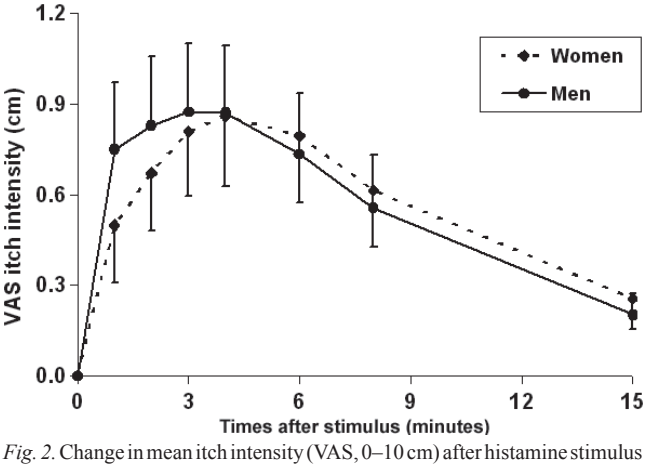

Fig. 2. Change in mean itch intensity (VAS, 0–10 cm) after histamine stimulus for women and men. Pooled data for all zones, (± standard error, $n=28$).

Table I. *Itch intensity (VAS cm) after 1 and 15 min following histamine stimulation, and maximum scores encountered, for women and men, in relation to the zone tested (1 and 2 = right; 3 and 4 = left) and the order of stimulation (1st, 2nd, 3rd, 4th).* n = *28,* [a]n = *112)*

Zone/order	1 min Mean ± SE	15 min Mean ± SE	Maximum Mean ± SE
Women			
Zone 1	0.54±0.17	0.29+0.09	1.10±0.21
Zone 2	0.39±0.20	0.31±0.11	1.10±0.27
Zone 3	0.64±0.27	0.18±0.06	1.24±0.31
Zone 4	0.42±0.13	0.25±0.14	1.01±0.24
All zones[a]	0.50±0.19	0.26±0.10	1.11±0.26
1st	0.48±0.18	0.45±0.16	1.33±0.29
2nd	0.60±0.20	0.22±0.08	1.34±0.29
3rd	0.31±0.09	0.16±0.06	0.78±0.14
4th	0.59±0.25	0.21±0.07	1.00±0.28
Men			
Zone 1	0.87±0.21	0.26±0.09	1.35±0.26
Zone 2	0.85±0.27	0.16±0.06	1.19±0.27
Zone 3	0.78±0.20	0.18±0.05	1.25±0.24
Zone 4	0.50+0.19	0.20±0.08	0.84±0.20
All zones[a]	0.75±0.22	0.20±0.07	1.16±0.24
1st	0.81±0.29	0.26+0.09	1.25±0.30
2nd	0.86±0.26	0.30±0.09	1.35±0.27
3rd	0.64+0.17	0.14±0.06	0.96±0.17
4th	0.68±0.19	0.12±0.05	1.07±0.23

but were not significantly different from each other. The intensity after 15 min had decreased to a near-zero value, which was significantly different from all the other time-points. The maximum intensity encountered was fairly low, and was similar for men and women (1.16 ± 0.24 cm and 1.11 ± 0.26 cm, respectively). From this time, the intensity gradually decreased to approximately 0.2 cm after 15 min.

Although itch intensity appears to be perceived earlier and to be higher for men than for women, this did not reach statistical significance.

For each group (men and women), the effect of zone was analysed. This was found to be non-significant in both groups (men, $p = 0.094$; women, $p = 0.935$) and also demonstrated no right–left side differences since zones 1/2 were on the right arm, and zones 3/4 on the left.

The rank or order of stimulation was also found to be non-significant, whether for men ($p = 0.287$) or for women ($p = 0.063$). Nonetheless, for both groups, the second stimulation was always perceived as the most intense and the third as the weakest (Table I).

PET brain activation study

From Table II it can be seen that the two stimuli (histamine and saline) were significantly different in terms of the itch sensation perceived ($p = 0.013$). Histamine produced greater intensities than saline, with VAS values around 1.5 and 0.5, respectively. The rank of application, for both stimuli, was not significant.

In terms of brain activation, histamine-saline rCBF comparisons demonstrated that the brain regions activated were located mainly in the right hemisphere ipsilateral to the site of stimulation (Fig. 3) and involved the paracentral gyrus/medial cingulate cortex (MCC) (BA 24/31), the inferior parietal lobe (BA 2/40) in both hemispheres, the posterior parietal lobe (BA 7), the cuneus and the precuneus. We also found activation in the medial temporal gyrus and the cerebellum, also in the right hemisphere, and some activation in the left insula (contralateral).

DISCUSSION

Histamine iontophoresis itch model

The purpose of our study was to develop a reliable model for itch induction that would be suitable for use in PET imaging. The results show that the maximal itch induced was fairly low in intensity, approximately 1.1 cm on the VAS, which peaked between 2 and 4 min, and which was independent of sex, zone, or the order of application. After 15 min, the intensity scores were very low (0.2) and significantly different from all the other time-points. Thus, from the study of the temporal characteristics of the itch sensation, we believe itch has effectively disappeared after 15 min.

In this respect, the temporal characteristics of the model make it suitable for PET- $H_2{}^{15}O$ studies. This is mainly for two reasons: (*i*) a single PET scan takes 2 min to perform, thus a stable significant itch sensation is needed during this time, and (*ii*) repeated stimulation periods of 15 min are required to optimize the use of the PET scanner in consideration of the subject's comfort.

However, our model, which applies a current charge of 3.84 mC induces itch that is low in intensity, with a maximum VAS of 0.9/10. This is quite weak in comparison with other work: 1.3 mC → 4/10 (8), 20 mC→5/10 (8), 6 mC → 2.5 /10 (10). Nonetheless, in another study by Yosipovitch et al. (11), similarly low itch intensities were reported with a VAS of 1.4/10 at 6 mC and that only 12 of the 21 subjects had itch VAS scores ≥ 1/10. It must also be borne in mind that the overall weak itch sensation reported is an average result, which does not reflect the inter-individual variability. Reactivity to histamine would undoubtedly depend on factors such as the density of the C fibre population, the physical parameters of barrier function of the stratum corneum or

Table II. *Visual analogue scale itch intensity scores in centimetres obtained after each positron emission tomography (PET) scan (*n = *14), with the mean of pooled data*

PET scan	Histamine Mean±SE	Saline control Mean±SE
1st	1.4±0.37	0.57+0.25
2nd	1.6+0.41	0.39+0.20
3rd	1.2+0.33	0.39±0.17
Mean	1.4±0.34	0.45±0.14

SE: standard error.

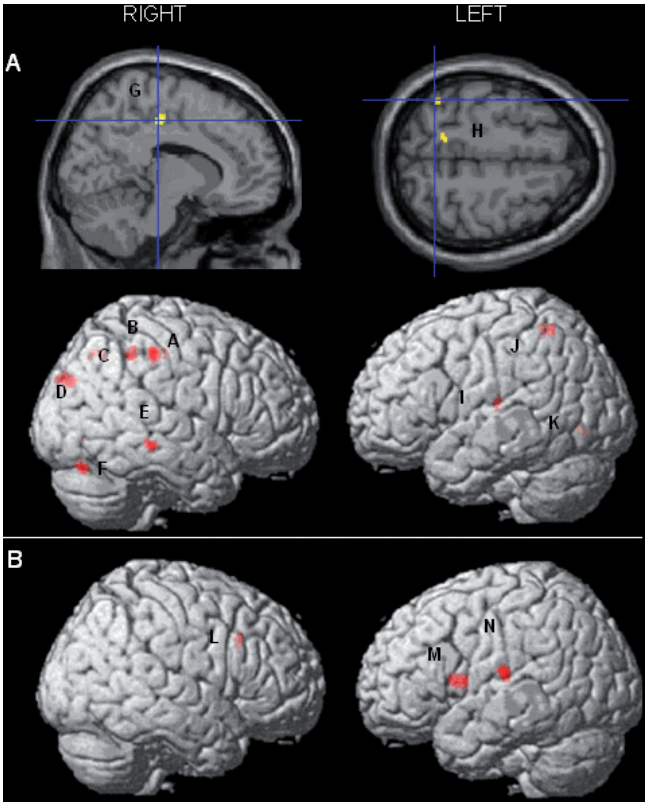

Fig. 3. (A) Cerebral location of areas of significant regional cerebral blood flow (rCBF) increase during histamine itch compared with saline control (uncorrected p-value <0.001). A = post-central gyrus BA 1/2 [60,–30,46], B = inferior parietal lobe BA 40 [46,–42,48], C = superior parietal lobe BA 7/precuneus [24,–62,46], D = cuneus BA 19/7 [28,–82,30], E = median temporal gyrus BA 21 [66,–32,–10], F = cerebellum [48,–74,–24], G = medium cingulate cortex BA 31 [12,–24,46], H = precuneus BA 7 [–14,–50,56], I = insula BA 13 [–46,–20,12], J = inferior parietal lobe BA 40 [–40,–56,58], K = lingual gyrus BA 18 [–4,–74,–6]. (B) Brain areas positively correlated with the unpleasantness of the itch sensation perceived (uncorrected p-value <0.001). L = anterior cingulate cortex BA 32 [16,20,36], M = anterior insula BA 13/44 [–42,12,10], N = posterior insula BA 41/43 [–48,–20,14].

its thickness. Some authors have suggested structuring the VAS scale for itch by defining a threshold where there is a desire to scratch, such as one-third of the VAS (6, 8). The VAS for itch in the present study was not structured in this way, being based on the assumption that an itch sensation, however low, presents a desire to scratch. This could explain the VAS scores obtained, which, although low in comparison with other similar studies, showed a significant variation with time.

We found no significant differences in itch ratings either for left-right comparisons, or for the order of testing. From the literature, investigations into these kinds of differences have focussed mainly on pain rather than itch. In a review by Merskey & Watson (13), the authors suggest a preponderance of pain for the left side of the body, citing work that has generally involved patients referred for psychiatric evaluation. However, in a survey on patients attending a pain clinic experiencing pain due to a variety of causes, the results contradicted those of Merskey & Watson (14), in that no predominance for one side over the other was found. Various hypotheses were put forward to explain this, among which was the different types of populations studied, either patients with psychological symptoms experiencing pain (13), or patients having pain from a variety of more physiological origins (14). Overall, there appears to be no convincing evidence for left-right effects with pain, and no proof of left-right differences with itch, which was confirmed by our data.

Furthermore, with regard to sex differences and itch, we also found this to be non-significant. Little is known about this, although histamine-induced wheal responses have been reported to be more pronounced in women than men, although itch did not vary (6). Sex differences for pain however, have been extensively reported. In a review by Fillingim et al. (15), females were found to be more sensitive to multiple pain modalities than men. With regard to pain induced experimentally by pressure, electricity, ischaemia, heat and cold, the majority of work quoted showed females to be more sensitive, with the exception of ischaemic pain which showed no differences. Our data on itch were thus in disagreement with these findings.

PET brain activation study

The behavioural results showed that histamine induced more intense itch than the control, and that the rank of stimulation did not alter this. With regard to central activation, the brain areas activated were similar to those reported in previous publications despite these using both different imaging techniques and modes of induction (2, 3, 16–21). This led us to conclude that our iontophoresis model of itch induction, which is simple and non-invasive, was suitable for this kind of cerebral activation study. A further advantage of this model is the possibility of modulating the histamine reaction by altering the amount of electric current or the duration of stimulus (6). In this way, the iontophoresis model may be adjusted to give different itch intensities, something that is not possible with the prick test method.

Activation ipsilateral and contralateral to the stimulation was found in the inferior parietal lobe (BA 2/40) in accordance with others studies on itch (3, 16, 18, 19, 21). Bilateral activation was found in the posterior parietal cortex (PPC) (BA 7), which has been described by Mochizuki et al. and Lekness (3, 20). The activation of only the right inferior parietal lobe (IPL), which is a main part of the PPC, is in accordance with the right hemispheric lateralization for somatospatial information (22). The parietal cortex also serves a crucial role in transforming sensory input into motor output (23), thus it must be engaged in premotor planning.

We also found activation in the cingulate cortex, which is known to be involved in emotion, cognition

and motor processing (24). Activation in the MCC or in the dorsal anterior cingulate cortex (dACC) has been described in previous itch studies (21). The dACC is also thought to be engaged in premotor planning (25, 26), as well as in stimulus intensity encoding (27, 28). Like Valet et al. (21), we hypothesize that the dual function of the dACC and the anatomical neighbouring to M1 is advantageous for the generation of an adequate motor response to the itching stimulus in relation to the processed sensory information. Activation was found in the right hemisphere, which reflects action of the left arm to alleviate itch sensation.

We found that activation in the ipsilateral anterior cingulate correlated with the intensity of the itch sensation perceived. Activation in our study is situated in the dorsal area of the ACC, more anterior than the activation previously described in the MCC. This kind of activation has already been described in previous itch studies (2, 16, 17, 19) and reflects the unpleasant nature of itch.

Activation was also found in the left insula contralateral to the stimulation. Itch sensation is mediated from the periphery by small diameter primary afferents, projecting to the insula, which has been found to be activated by itching stimulus (20, 29, 30). Its involvement varies with the type of stimulus and the intensity (20). In the present study we used a histamine concentration of 1%, which induced insula activation in the left hemisphere. It has been shown to be activated in response to itch in previous studies that used histamine concentrations of $\leq$8% (17, 18, 20), but not in two studies where lower concentrations ($\leq$0.01%) were used (3, 19).

In previous studies, only the posterior part of the insula has been found to be correlated with itch unpleasantness (2, 17), but in our correlation study the two parts are activated.

Thus, our model has been tested in a behavioural study and a neuroimaging study with PET and seems to be reliable for this kind of neuroimaging approach.

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