Itch Matrixes

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Keywords: itch, matrix, pain, brain, imaging

INTRODUCTION

In a recent meta-analysis from our group based on a systematic review we have identified brain regions reported to be responsible for central mechanisms of itch processing (1). We also have discussed the central mechanisms of itch proceeding in the brain more in depth in a review paper (2). The research papers that have studied central mechanism of itch are presented in Table 1 while their results are presented in Table 2. Here in this paper, we are exploring a new idea in which we categorize the itch matrix in the brain into three matrices that each of them is contributing to a specific aspect of itch perception. This conceptualizes the processing of itch signals into different itch matrices could be useful in order to model different aspects of itch. For example, it is possible, that an overactivity in second matrix cause a higher susceptibility to contagious itch.

Unlike the visual system pain and itch can evoke multitude of regions in the brain, which we call pain matrix and itch matrix respectively. Recent studies have proposed that the pain matrix can be categorized into three different pain matrixes (40, 41): one contributing to perception and the location of pain; another matrix responsible for the affective aspect of the pain; and a third involving decoding the cognitive aspect of pain. In the same manner, we guardedly propose that the itch processing network can be broken down into three main matrixes although many data are still lacking. These three matrixes have been presented in Figure 1.

FIRST ITCH MATRIX

The first itch matrix includes but is not restricted to the primary sensorimotor cortex, the parietal/central operculum, and the posterior insular cortex (Figure 2A).

Among these three regions the primary sensorimotor cortex is involved in the encoding of the recognition, localization, and intensity of painful stimuli (42). In pain studies, activation in this region bears a linear relationship with pain intensity (43–47). In a positron emission tomography (PET) study by Drzezga et al. (5) the authors reported that SI activity, is positively correlated with itch intensity. Six years after Drzezga, in 2007, Mochizuki et al. added the secondary somatosensory cortex (SII) demonstrating an increase of activity in this region after itch induction with histamine (10). The increase was statistically not different than the proven one observed in the painful condition (pain vs. itch) but did not reach a statistically corrected threshold when comparing itch against no itch.

In another study which includes both AD patients and healthy controls, itch was found to activate the post-central gyrus in the right hemisphere (12). This study together with Drzezga study in 2001 are reported in the meta-analysis on Itch from Lee et al. (48). Out of 56 regions listed in the parietal cortex (31 Left and 25 Right) from 18 studies (Table 1). Brain activity upon itch stimulation,
in (48), left SI appears to be activated eight times against two only in the right hemisphere. On the contrary, right SII is reported five times against two only in the left hemisphere. The other regions mentioned (n = 39) are in both left and right parietal cortices sometime very near to the SI/SII regions (i.e., SMG, SPL, IPL, anterior parietal cortex).

In the meta-analysis from Roberts et al. (49), the authors suggest the possibility of a specificity of these regions for the itching process as they appear to be better activated by itching than by pain. Interestingly, they also group these regions with the central operculum. In a recent meta-analysis of our group (1), SI/SII region was not clearly identified but we discussed this point regarding the diversity of studies we included. Our results on correlations with itch intensity also showed two important clusters in bilateral insular cortices (5068 voxels right 4589 voxels left) that spread to a great extent on the post-central gyri.

The co-activation of the central operculum together with SI/SII cortex is widely reported in itch literature both in healthy subjects and patients. Indeed, central operculum corresponding to the junction of pre- and post-central gyri accompanied with the region located laterally to the posterior convolution of the insula is often confounded with insula itself or even SI. In the regions abbreviated OPC, also named rolandic operculum elsewhere, itch intensity was also correlated with PET signal both in healthy subjects and AD patients (4, 33).

Finally, we propose that the insular cortex, and especially its anterior portion, takes part into this first matrix. As a common point between these regions, their gradual response with itch intensity seems important to highlight. In Leknes et al. bilateral insular and left posterior insular activity (BOLD) is correlated with histamine-induced itch intensity (9). Following Craig (50, 51), Mochizuki et al. postulate that the posterior part of insula plays a different role than its anterior part (52, 53). A distinction that can also find its basis on cytoarchitectural composition of these structures and their connectives with other brain areas (50, 54).

Despite weak evidences in itch literature, other evidences can help to understand the insula role in processing the sensations which are common to itch and pain. Mazzola et al. explain that the two thirds of posterior insula submitted to low electrical stimulation (SEEG) directly translate these stimulations as pain sensations (55). Another study from Frot et al. showed that once pain feeling is reached, the posterior insular cortex activity still correlates with noxious thermal stimulation intensity (47).

In summary, all these regions encode the feeling of itchy sensation and are somewhat translating its intensity level as well as their location following a somatotopic representation. When compared to Xiang et al. study (41), this first matrix includes all already reported regions for pain. However, studies reporting activities in those regions only for itch are rare and some studies need to be carefully interpreted given approximations inherent to main peak reporting. Effectively, secondary peaks of wide clusters or percentage of anatomical regions covered by these clusters are most often not indicated. As an example, the absence of parietal operculum in Roberts et al. study (49) needs to be put in perspective. Indeed, the point that the contrast pain—itch shows an increased activity in the parietal operculum does not mean that this region is silent in itch. Moreover, in the same study, the opposite contrast itch—pain, which reveals an implication of both right supramarginal gyrus and central operculum, could have led us to add more parietal areas to this first matrix.

So far, we have dealt with the membership of each of these brain regions in the matrix separately. However, interesting arguments reside in the fact that new pathological conditions can appear when these regions grouped and malfunction together. Hence, some studies reported that SI/SII together with the insular cortex participate in creating the allodynia phenomenon (56–59). Consecutively, these regions once activated lead to an ignition of the pain network inducing activity in the PAG, the prefrontal cortex, the thalamus, the amygdala, the ACC and many other regions within the pain network. Allodynia has repercussions on the way normal brain areas react to tactile stimuli and authors do not only consider the condition through the scope of pain matrix. Many brain areas are those involved in tactile or thermal sensitivity and this allows more faithful comparison with itch perception. The difficulty with allodynia is that even when it is spontaneous, painful sensation is quickly reached and its intensity then depends on other brain region listed above.

To illustrate this phenomenon, we adduce together both Ducreux et al. study (60) and an article from Geuter et al. (61) about predictive coding. In Ducreux et al. authors demonstrated with noxious and non-noxious cold stimulation (4° and 22°C) that while non-noxious cold in control subjects activates SII and the insular cortex (mostly its anterior part), the same non-noxious stimulation did activates SII and mid-posterior insula in allodynic patients together with other regions of the pain network (60). In Geuter et al. work, the authors used the predictive coding theory of brain functioning to demonstrate a difference within the anterior and the posterior part of the insula. While the anterior part would be dedicated to pain feelings as a prediction error on perceived sensations, the posterior part only responds to pain intensity with no comparisons to any predicted sensation (61). We propose that in Ducreux et al. even if the feeling is non-noxious in control subjects, it remains unpredictable and then activates the anterior part of the insula. However, allodynic patients are prepared to feel painful

**Abbreviations**: ACC, Anterior Cingulate Cortex; AD, Atopic Dermatitis; aIC, Anterior part of the Insular Cortex; aMCC, Anterior part of the Middle Cingulate Cortex; BOLD, Blood Oxygenation Level Dependent; dACC, Dorsal part of the Anterior Cingulate Cortex; DLPFC, Dorso-Lateral Prefrontal Cortex; IPL, Inferior Parietal Lobule; OPC, Operculum Central; PAG, Peri-Aqueductal Gray matter; PCC, Posterior Cingulate Cortex; PET, Positron Emission Tomography; pIC, Posterior Insular Cortex; pMCC, Posterior part of the Middle Cingulate Cortex; SI, Primary Somatosensory cortex; SII, Secondary Somatosensory cortex; SEEG, Stereo-Electro-Encephalo-Graphy; SMG, Supra-Marginal Gyrus; SPL, Superior Parietal Lobule.
### TABLE 1 | Papers and methods which have been used in order to study central mechanism of itch.

| #  | References            | Scanner | Neuroimaging analysis | Itch induction   | Itch stimulus | Number of subjects | Pathology       | Comments         |
|----|-----------------------|---------|-----------------------|------------------|---------------|-------------------|-----------------|-----------------|
| 1  | Hsieh et al. (3)      | PET     | Subtraction           | Intracutaneous injection | Histamine     | 10                | Healthy         |                 |
| 2  | Darsow et al. (4)     | PET     | Subtraction           | Skin prick        | Histamine     | 6                 | Healthy         |                 |
| 3  | Darsow et al. (4)     | PET     | Correlation           | Skin prick        | Histamine     | 6                 | Healthy         |                 |
| 4  | Drzezga et al. (5)    | PET     | Correlation           | Skin prick        | Histamine     | 6                 | Healthy         |                 |
| 5  | Mochizuki et al. (6)  | PET     | Subtraction           | Iontophoresis     | Histamine     | 15                | Healthy         |                 |
| 6  | Walter et al. (7)     | fMRI    | Correlation           | Skin prick        | Histamine     | 6                 | Healthy         |                 |
| 7  | Herde et al. (8)      | fMRI    | Subtraction           | Intracutaneous microdialysis | Histamine     | 10                | Healthy         |                 |
| 8  | Leknes et al. (9)     | fMRI    | Correlation           | Skin prick        | Histamine     | 8                 | Healthy         |                 |
| 9  | Leknes et al. (9)     | fMRI    | Correlation           | Allergan          |              | 8                 | Atopic cohort    |                 |
| 10 | Mochizuki et al. (10) | fMRI    | Correlation           | Iontophoresis     | Histamine     | 14                | Healthy         |                 |
| 11 | Mochizuki et al. (10) | fMRI    | Subtraction           | Iontophoresis     | Histamine     | 14                | Healthy         |                 |
| 12 | Valet et al. (11)     | fMRI    | Subtraction           | Skin prick        | Histamine     | 12                | Healthy         |                 |
| 13 | Valet et al. (11)     | fMRI    | Subtraction           | Skin prick        | Histamine     | 12                | Healthy         | Temperature modeling |
| 14 | Schneider et al. (12) | PET     | Subtraction           | Iontophoresis     | Histamine     | 6                 | Healthy         |                 |
| 15 | Schneider et al. (12) | PET     | Subtraction           | Iontophoresis     | Histamine     | 8                 | Atopic dermatitis |                 |
| 16 | Schneider et al. (12) | PET     | Subtraction           | Iontophoresis     | Histamine     | 8                 | Healthy <-> AD |                 |
| 17 | Yosipovitch et al. (13)| fMRI | Subtraction           | Scratching        |              | 13                | Healthy         |                 |
| 18 | Ishiuji et al. (14)   | fMRI    | ASL                  | Iontophoresis     | Histamine     | 8                 | Atopic dermatitis |                 |
| 19 | Ishiuji et al. (14)   | fMRI    | ASL                  | Iontophoresis     | Histamine     | 7                 | Healthy         |                 |
| 20 | Ishiuji et al. (14)   | fMRI    | ASL                  | Iontophoresis     | Histamine     | 7                 | Healthy <-> AD |                 |
| 21 | Mochizuki et al. (15) | fMRI    | Subtraction           | Electrically induced itch | Histamine     | 10                | Healthy         |                 |
| 22 | Mochizuki et al. (15) | MEG     | Subtraction           | Electrically induced itch | Histamine     | 10                | Healthy         |                 |
| 23 | Vierow et al. (16)    | fMRI    | Subtraction           | Scratching        |              | 15                | Healthy         |                 |
| 24 | Vierow et al. (16)    | fMRI    | Subtraction           | Scratching in presence of itch | Histamine     | 15                | Healthy         |                 |
| 25 | Pfab et al. (17)      | fMRI    | Subtraction           | Skin prick non lesion skin | Histamine     | 13                | Atopic dermatitis | Thermal modulation |
| 26 | Pfab et al. (17)      | fMRI    | Subtraction           | Skin prick lesion skin | Histamine     | 13                | Atopic dermatitis | Thermal modulation |
| 27 | Bergeret et al. (18)  | PET     | Subtraction           | Iontophoresis     | Histamine     | 28                | Healthy         |                 |
| 28 | Bergeret et al. (18)  | PET     | Correlation           | Iontophoresis     | Histamine     | 29                | Healthy         | Itch sensation |
| 29 | Holle et al. (19)     | fMRI    | Subtraction           | Audiovisual itch |              | 18                | Healthy         |                 |
| 30 | Holle et al. (19)     | fMRI    | Correlation           | Audiovisual itch |              | 19                | Healthy         |                 |
| 31 | Keyn et al. (20)      | fMRI    | Subtraction           | Skin prick        | Histamine     | 16                | Healthy         |                 |
| 32 | Keyn et al. (20)      | fMRI    | Correlation           | Skin prick        | Histamine     | 16                | Healthy         |                 |
| 33 | Papoiu et al. (21)    | fMRI    | ASL                  | Iontophoresis     | Histamine     | 15                | Healthy         |                 |
| 34 | Papoiu et al. (21)    | fMRI    | ASL                  | Spiques rubbing   | Cowhage       | 15                | Healthy         |                 |
| #  | References                  | Scanner | Neuroimaging analysis | Itch induction          | Itch stimulus          | Number of subjects | Pathology          | Comments                                      |
|----|-----------------------------|---------|-----------------------|-------------------------|------------------------|--------------------|-------------------|-----------------------------------------------|
| 35 | Papoiu et al. (21)          | fMRI    | ASL                   |                         |                        | 15                 | Healthy           | Cowhage <> Histamine                           |
| 36 | Papoiu et al. (21)          | fMRI    | Subtraction           | Audiovisual pain        |                        | 18                 | Healthy           | Itch & Pain                                    |
| 37 | Papoiu et al. (21)          | fMRI    | Subtraction           | Itch & Pain             |                        | 18                 | Healthy           | Correlated with the pleasurability            |
| 38 | Papoiu et al. (22)          | fMRI    | ASL-correlation       | Scratching              |                        | 14                 | Healthy           | Correlated with itch relief                   |
| 39 | Papoiu et al. (22)          | fMRI    | ASL-correlation       | Scratching              |                        | 14                 | Healthy           | Female>Males                                   |
| 40 | Stumpf et al. (23)          | fMRI    | Subtraction           | Microdialysis           | Histamine              | 33                 | Healthy           | Temperature modeling                           |
| 41 | Stumpf et al. (23)          | fMRI    | Subtraction           | Microdialysis           | Histamine              | 33                 | Healthy           | Temperature modeling and acupuncture intervention |
| 42 | Napadow et al. (24)         | fMRI    | Subtraction           | Skin prick              | Allergen-induced      | 14                 | Atopic dermatitis | Right premotor as seed                         |
| 43 | Napadow et al. (24)         | fMRI    | Subtraction           | Skin prick              | Allergen-induced      | 14                 | Atopic dermatitis | Right insula as seed                           |
| 44 | Desbordes et al. (25)       | fMRI    | Connectivity         | Skin prick              | Allergen-induced      | 14                 | Atopic dermatitis | Left superior parietal lobule as seed          |
| 45 | Desbordes et al. (25)       | fMRI    | Connectivity         | Skin prick              | Allergen-induced      | 14                 | Atopic dermatitis | Right anterior mid-cingulate cortex as seed    |
| 46 | Desbordes et al. (25)       | fMRI    | Connectivity         | Skin prick              | Allergen-induced      | 14                 | Atopic dermatitis | Right caudate as seed                          |
| 47 | Desbordes et al. (25)       | fMRI    | Connectivity         | Skin prick              | Allergen-induced      | 14                 | Atopic dermatitis | Right globus pallidus                         |
| 48 | Desbordes et al. (25)       | fMRI    | Connectivity         | Skin prick              | Allergen-induced      | 14                 | Atopic dermatitis | Scratching itch                                |
| 49 | Desbordes et al. (25)       | fMRI    | Connectivity         | Skin prick              | Allergen-induced      | 14                 | Atopic dermatitis | Scratching itch                                |
| 50 | Desbordes et al. (25)       | fMRI    | Connectivity         | Skin prick              | Allergen-induced      | 14                 | Atopic dermatitis | Scratching itch                                |
| 51 | Mochizuki et al. (28)       | fMRI    | Subtraction           | Electrically induced itch| Passive scratching     | 16                 | Healthy           | Deactivation scratching itch region            |
| 52 | Mochizuki et al. (28)       | fMRI    | Subtraction           | Electrically induced itch| Passive scratching     | 16                 | Healthy           | Scratching itch                                |
| 53 | Mochizuki et al. (28)       | fMRI    | Subtraction           | Electrically induced itch| Passive scratching     | 16                 | Healthy           | Scratching itch                                |
| 54 | Mochizuki et al. (28)       | fMRI    | Subtraction           | Electrically induced itch| Passive scratching     | 16                 | Healthy           | Scratching itch                                |
| 55 | Mochizuki et al. (28)       | fMRI    | Subtraction           | Electrically induced itch| Passive scratching     | 16                 | Healthy           | Scratching itch                                |
| 56 | Papoiu et al. (27)          | fMRI    | ASL                   | Iontophoresis           | Histamine              | 13                 | End-stage renal disease                      | (Continued)
| #  | References          | Scanner | Neuroimaging analysis | Itch induction       | Itch stimulus | Number of subjects | Pathology                        | Comments                                                                 |
|----|---------------------|---------|-----------------------|----------------------|---------------|-------------------|----------------------------------|--------------------------------------------------------------------------|
| 57 | Papoiu et al. (27)  | fMRI    | ASL                   | Spicules rubbing     | Cowhage       | 13                | End-stage renal disease          |                                                                           |
| 58 | Kim et al. (28)     | fMRI    | Subtraction           | Audiovisual itch     |               | 14                | Neurodermatosis                  | Stress-induced pruritus                                                  |
| 59 | Kim et al. (28)     | fMRI    | Subtraction           | Audiovisual itch     |               | 14                | Neurodermatosis                  | Stress-induced pruritus (after sedating antihistamine treatment)         |
| 60 | Kim et al. (28)     | fMRI    | Subtraction           | Audiovisual itch     |               | 14                | Neurodermatosis                  | Stress-induced pruritus (after non-sedating antihistamine treatment)     |
| 61 | Mochizuki et al. (29)| fMRI    | ASL                   | Spicules rubbing     | Cowhage       | 10                | Healthy                         | Scratching                                                               |
| 62 | Mochizuki et al. (29)| fMRI    | ASL                   | Spicules rubbing     | Cowhage       | 10                | Chronic itch patients            | Scratching                                                               |
| 63 | Mochizuki et al. (29)| fMRI    | ASL                   | Spicules rubbing     | Cowhage       | 20                | Patients > Healthy               | Scratching                                                               |
| 64 | Mochizuki et al. (29)| fMRI    | ASL                   | Spicules rubbing     | Cowhage       | 10                | Healthy                         | Scratching                                                               |
| 65 | Mochizuki et al. (29)| fMRI    | ASL                   | Spicules rubbing     | Cowhage       | 10                | Chronic itch patients            | Scratching                                                               |
| 66 | Mochizuki et al. (29)| fMRI    | ASL                   | Spicules rubbing     | Cowhage       | 20                | Patients > Healthy               | Scratching                                                               |
| 67 | Napadow et al. (30) | fMRI    |                       | Skin prick           | Allergan      | 14                | Atopic dermatitis                | Nocebo > open saline                                                     |
| 68 | Papoiu et al. (31)  | fMRI    | ASL                   | Iontophoresis Histamine| 24            | Healthy            | Areas significantly activated during the suppression of histamine itch by butorphanol | Deactivation areas significantly correlated with the reduction in cowhage itch |
| 69 | Papoiu et al. (31)  | fMRI    | ASL                   | Spicules rubbing     | Cowhage       | 25                | Healthy                         | Placebo                                                                  |
| 70 | Vierow et al. (32)  | fMRI    | Subtraction           | Spicules rubbing     | Capsaicin     | 16                | Healthy                         | Placebo                                                                  |
| 71 | Vierow et al. (32)  | fMRI    | Subtraction           | Spicules rubbing     | Capsaicin     | 16                | Healthy                         | Naltrexone                                                               |
| 72 | Vierow et al. (32)  | fMRI    | Subtraction           | Spicules rubbing     | Histamine     | 16                | Healthy                         | Placebo                                                                  |
| 73 | Vierow et al. (32)  | fMRI    | Subtraction           | Spicules rubbing     | Histamine     | 16                | Healthy                         | Naltrexone                                                               |
| 74 | Schut et al. (33)   | fMRI    | ASL-Subtraction       | Audiovisual          |               | 11                | Atopic dermatitis                |                                                                          |
| 75 | Schut et al. (33)   | fMRI    | ASL-correlation       | Audiovisual          |               | 11                | Atopic dermatitis                |                                                                          |
| #  | References                | Scanner | Neuroimaging analysis | Itch induction | Itch stimulus | Number of subjects | Pathology | Comments                                                                 |
|----|---------------------------|---------|-----------------------|----------------|---------------|------------------|-----------|---------------------------------------------------------------------------|
| 76 | Stumpf et al. (34)        | fMRI    | Subtraction           | Microdialysis  | Histamine     | 33               | Healthy | Itch modulation by distraction (Itch > stroop)                             |
| 77 | van de Sand et al. (35)   | fMRI    | Subtraction           | Skin patch     | Histamine     | 30               | Healthy | Nocebo modulation Itch-nocebo > itch only (temperature modulating)        |
| 78 | van de Sand et al. (35)   | fMRI    | Connectivity with insula | Skin patch     | Histamine     | 30               | Healthy | Nocebo modulation Itch-nocebo > itch only (temperature modulating)        |
| 79 | Wang et al. (36)          | fMRI    | Resting state         |                |               | 40+40            | Chronic urticaria +Healthy | CSU > HC (amplitude of low frequency fluctuations)                       |
| 80 | Wang et al. (36)          | fMRI    | Resting state         |                |               | 40+40            | Chronic urticaria +Healthy | CSU > HC (functional connectivity with right ventral striatum)           |
| 81 | Wang et al. (36)          | fMRI    | Resting state         |                |               | 40+40            | Chronic urticaria +Healthy | CSU > HC (functional connectivity with right putamen)                    |
| 82 | Wang et al. (37)          | fMRI    | Resting state         |                |               | 40+40            | Chronic urticaria +Healthy | CSU > HC (regional homogeneity)                                          |
| 83 | Wang et al. (37)          | fMRI    | Resting state         |                |               | 40               | Chronic urticaria +Healthy | After intervention > Before intervention (regional homogeneity)          |
| 84 | Wang et al. (37)          | fMRI    | Resting state         |                |               | 40+40            | Chronic urticaria +Healthy | CSU > HC (functional connectivity with Cerebellum)                       |
| 85 | Wang et al. (37)          | fMRI    | Resting state         |                |               | 40               | Chronic urticaria +Healthy | After intervention > Before intervention (functional connectivity with Cerebellum) |

(Continued)
TABLE 1 | Continued

| #  | References         | Scanner | Neuroimaging analysis | Itch induction | Itch stimulus | Number of subjects | Pathology | Comments |
|----|--------------------|---------|------------------------|----------------|---------------|-------------------|-----------|----------|
| 86 | Wang et al. (37)   | fMRI    | Resting state          |                |               | 40                | Chronic urticaria | After intervention > Before intervention (functional connectivity with S1/M1/SMA) |
| 87 | Min et al. (38)    | fMRI    | Resting state          | Skin prick     | Histamine     | 20                | Healthy   | Acupuncture (itch-baseline) > Non-responder (itch-baseline) (functional connectivity with left Putamen) |
| 88 | Min et al. (38)    | fMRI    | Resting state          | Skin prick     | Histamine     | 20                | Healthy   | Acupuncture (itch-baseline) > Non-responder (itch-baseline) (functional connectivity with right Putamen) |
| 89 | Min et al. (38)    | fMRI    | Resting state          | Skin prick     | Histamine     | 20                | Healthy   | Acupuncture (itch-baseline) > Non-responder (itch-baseline) (functional connectivity with Pallidum) |
| 90 | Mochizuki et al. (39) | fMRI  | Subtraction            | Electrically induced itch |               | 25                | Healthy   |                     |
| 91 | Mochizuki et al. (39) | fMRI  | Connectivity           | Electrically induced itch |               | 25                | Healthy   |                     |

stimulation and then, the anterior part shut down as painful sensation are correctly predicted. Meanwhile, the posterior part of the insula starts to encode its intensity like it was demonstrated by Frot et al. (47) in implanted subjects when stimulation becomes noxious.

SECOND ITCH MATRIX

The second itch matrix could consist of the ACC, aMCC, aIC, amygdala, striatum and hippocampus (Figure 2B). This network could encode the affective and motivational aspects of itch. Significant activation in the ACC, especially dorsal, extending to the anterior part of the middle cingulate cortex (aMCC), has been linked to the reward network and the positive or negative emotional response (40). Noteworthy, Vogt has reported that the aMCC reflects emotional awareness and fear leading to the questioning of the enrolment of the aMCC to the ACC gross function (62, 63). Considering the anterior insula, it is reported to be involved in the awareness of emotions and subjective feelings (50) as well as errors of predictions like mentioned above. Another literature about lesions in the aIC would cause deficits in emotional awareness (e.g., alexithymia) (64). Several studies have reported that activity in the aIC is significantly correlated with the unpleasantness of itch (8–10, 18, 21). For the hippocampus, it has been also shown that this structure is fully integrated in the itch network (13, 21, 22). For example, only active scratching can relief activity in ipsi-hippocampal structure (53). The role of hippocampus together with amygdala, dACC and insular cortex are well-documented in Sanders and Akiyama (65). The authors noticed and argued that “amygdala and hippocampus activation appears to go hand-in-hand in most studies of itch, suggesting that the memory of previous itch experiences may be a significant factor in itch-related anxiety.” Stratum possibly
TABLE 2 | Results of the all the papers studied the central mechanism of itch.

| Region | Author |
|--------|--------|
| Primary somatosensory cortex (BA 1, 2, 3) | 1 |
| Somatosensory associated/parietal cortex (BA 5, 7) | 2, Darsow et al. (4) |
| Primary motor cortex (BA 4) | 3, Darsow et al. (4) |
| Pre- motor and supplementary motor cortex (BA 6) | 4, Drzezga et al. (5) |
| Cerebellum | 5, Mochizuki et al. (6) |
| Insular cortex (BA 13, 16) | 6, Walter et al. (7) |
| Posterior cingulate cortex (BA 23, 31) | 7, Herde et al. (8) |
| Anterior cingulate cortex (BA 24, 32, 33) | 8, Leknes et al. (9) |
| Prefrontal cortex (BA 9) | 9, Leknes et al. (9) |
| Frontopolar and orbital area (BA 8, 10, 11, 12) | 10, Mochizuki et al. (10) |
| Inferior and dorsolateral prefrontal cortex (BA 44, 45, 46, 47) | 11, Mochizuki et al. (10) |
| Temporal gyrus (BA 20, 21, 22, 38) | 12, Valet et al. (11) |
| Fusiform | |
| Parietal pole/Wernicke's area (BA 39, 40) | 13, Valet et al. (11) |
| Inferior parietal, supramarginal | |
| Thalamus | |
| Basal ganglia | 14, Schneider et al. (12) |
| Secondary somatosensory cortex (BA 40, 41) | 15, Schneider et al. (12) |
| Precuneus (BA 7, 35) | 16, Schneider et al. (12) |
| Putamen | |
| Visual association gyrus (BA 17, 18, 19) | 17, Yosipovitch et al. (13) |
| Anterior entorhinal cortex (BA 34) | 18, Ishiuji et al. (14) |
| Hippocampus | 19, Ishiuji et al. (14) |
| Parahippocampal gyrus | 20, Ishiuji et al. (14) |
| Ventral tegmental area cum om | 21, Mochizuki et al. (15) |
| Ventral tegmental area | 22, Mochizuki et al. (15) |
| Raphé nucleus | 23, Vierow et al. (16) |
| Red Nucleus | 24, Vierow et al. (16) |
| PAG | |
| Substantia nigra | |
| Ciastrum | |
| Midbrain | |
| Amygdala | |
| Brain stem | |
| Lentiform nucleus | |
| Pons | |
### TABLE 2

| Regions                                                                 | Authors                        |
|------------------------------------------------------------------------|--------------------------------|
| Primary somatosensory cortex (BA 1, 2, 3)                              | Bergeret et al. (18)           |
| Somatosensory associated/parietal cortex (BA 5, 7)                     | Holle et al. (19)              |
| Primary motor cortex (BA 4)                                           | Holle et al. (19)              |
| Pre- motor and supplementary motor cortex (BA 6)                      | Kleyn et al. (20)              |
| Cerebellum                                                            | Papoiu et al. (21)             |
| Insular cortex (BA 13, 16)                                            | Papoiu et al. (21)             |
| Posterior cingulate cortex (BA 23, 31)                                | Papoiu et al. (21)             |
| Anterior cingulate cortex (BA 24, 32, 33)                             | Papoiu et al. (21)             |
| Prefrontal cortex (BA 9)                                              | Papoiu et al. (21)             |
| Frontopolar and orbifrontal area (BA 8, 10, 11, 12)                   | Papoiu et al. (21)             |
| Inferior and dorsolateral prefrontal cortex (BA 44, 45, 46, 47)       | Papoiu et al. (21)             |
| Temporal gyrus (BA 20, 21, 22, 38)                                    | Papoiu et al. (21)             |
| + fusiform                                                             |                                |
| Prietal pole/Wernicke's area (BA 39, 40)                               | Papoiu et al. (21)             |
| Inferior parietal, supramarginal                                      |                                |
| Thalamus                                                               |                                |
| Basal ganglia                                                          |                                |
| Secondary somatosensory cortex (BA 40, 43)                            | Stumpf et al. (23)             |
| Precuneus (BA 7, 31)                                                  | Stumpf et al. (23)             |
| Putamen                                                                | Desbordes et al. (25)          |
| Visual association gyrus (BA 17, 18, 19)                               | Desbordes et al. (25)          |
| Anterior entorhinal cortex (BA 34)                                     | Desbordes et al. (25)          |
| Hippocampus                                                           | Desbordes et al. (25)          |
| Parahippocampal gyrus                                                 | Desbordes et al. (25)          |
| Ventral tegmental area (cum om ventral tegmental area)                | Desbordes et al. (25)          |
| Raphé nucleus                                                         | Desbordes et al. (25)          |
| Red Nucleus                                                           | Desbordes et al. (25)          |
| PAG                                                                    | Desbordes et al. (25)          |
| Substantia nigra                                                       | Desbordes et al. (25)          |
| Caudate                                                                | Desbordes et al. (25)          |
| Midbrain                                                              | Desbordes et al. (25)          |
| Amygdala                                                              | Desbordes et al. (25)          |
| Brain stem                                                            | Desbordes et al. (25)          |
| Lentiform nucleus                                                      | Desbordes et al. (25)          |
| Pons                                                                   | Desbordes et al. (25)          |
| Occipital                                                             | Desbordes et al. (25)          |
| Anterior cingulate cortex (BA 24, 32, 33)                             | Mochizuki et al. (26)          |
| Basal ganglia                                                          | Mochizuki et al. (26)          |
| Secondary somatosensory cortex (BA 40, 43)                            | Mochizuki et al. (26)          |
| Precuneus (BA 7, 31)                                                  | Mochizuki et al. (26)          |
| Putamen                                                                | Mochizuki et al. (26)          |
| Visual association gyrus (BA 17, 18, 19)                               | Mochizuki et al. (26)          |
| Anterior entorhinal cortex (BA 34)                                     | Mochizuki et al. (26)          |
| Hippocampus                                                           | Mochizuki et al. (26)          |
| Parahippocampal gyrus                                                 | Mochizuki et al. (26)          |
| Ventral tegmental area (cum om ventral tegmental area)                | Mochizuki et al. (26)          |
| Raphé nucleus                                                         | Mochizuki et al. (26)          |
| Red Nucleus                                                           | Mochizuki et al. (26)          |
| PAG                                                                    | Mochizuki et al. (26)          |
| Substantia nigra                                                       | Mochizuki et al. (26)          |
| Caudate                                                                | Mochizuki et al. (26)          |
| Midbrain                                                              | Mochizuki et al. (26)          |
| Amygdala                                                              | Mochizuki et al. (26)          |
| Brain stem                                                            | Mochizuki et al. (26)          |
| Lentiform nucleus                                                      | Mochizuki et al. (26)          |
| Pons                                                                   | Mochizuki et al. (26)          |
| Occipital                                                             | Mochizuki et al. (26)          |
| Anterior cingulate cortex (BA 24, 32, 33)                             | Papoiu et al. (21)             |
| Basal ganglia                                                          | Papoiu et al. (21)             |
| Secondary somatosensory cortex (BA 40, 43)                            | Papoiu et al. (21)             |
| Precuneus (BA 7, 31)                                                  | Papoiu et al. (21)             |
| Putamen                                                                | Papoiu et al. (21)             |
| Visual association gyrus (BA 17, 18, 19)                               | Papoiu et al. (21)             |
| Anterior entorhinal cortex (BA 34)                                     | Papoiu et al. (21)             |
| Hippocampus                                                           | Papoiu et al. (21)             |
| Parahippocampal gyrus                                                 | Papoiu et al. (21)             |
| Ventral tegmental area (cum om ventral tegmental area)                | Papoiu et al. (21)             |
| Raphé nucleus                                                         | Papoiu et al. (21)             |
| Red Nucleus                                                           | Papoiu et al. (21)             |
| PAG                                                                    | Papoiu et al. (21)             |
| Substantia nigra                                                       | Papoiu et al. (21)             |
| Caudate                                                                | Papoiu et al. (21)             |
| Midbrain                                                              | Papoiu et al. (21)             |
| Amygdala                                                              | Papoiu et al. (21)             |
| Brain stem                                                            | Papoiu et al. (21)             |
| Lentiform nucleus                                                      | Papoiu et al. (21)             |
| Pons                                                                   | Papoiu et al. (21)             |
| Occipital                                                             | Papoiu et al. (21)             |

(Continued)
TABLE 2 | Continued

| Parts of which matrix | 1 | 1/2 | 2 | 3 | 3 | 3 | 3 | 3 | 2 | 1 | 2 | 2 |
|-----------------------|---|-----|---|---|---|---|---|---|---|---|---|---|
| Regions               |   |     |   |   |   |   |   |   |   |   |   |   |
| Primary somatosensory cortex (BA 1, 2, 3) | B | B | L | L | B | R | B | L | B | L | L |
| Lateral somatosensory cortex (BA 3, 1%2) | D | D | D | D | D | D | D | D | D | D | D | D |
| Primary motor cortex (BA 4) | B | B | L | L | B | L | L | B | B | B | B | B |
| Premotor and supplementary motor cortex (BA 6) | B | B | R | B | B | B | B | B | B | B | B | B |
| Cerebellum | B | B | R | B | B | B | B | B | B | B | B | B |
| Insular cortex (BA 13, 16) | B | B | R | B | B | B | B | B | B | B | B | B |
| Posterior cingulate cortex (BA 23, 31) | B | B | R | B | B | B | B | B | B | B | B | B |
| Anterior cingulate cortex (BA 24, 32, 33) | B | B | R | B | B | B | B | B | B | B | B | B |
| Prefrontal cortex (BA 9) | B | B | R | B | B | B | B | B | B | B | B | B |
| Frontopolar and orbifrontal area (BA 8, 10, 11, 12) | B | B | R | B | B | B | B | B | B | B | B | B |
| Inferior and dorsolateral prefrontal cortex (BA 10, 11, 12) | B | B | R | B | B | B | B | B | B | B | B | B |
| Temporal gyrus (BA 20, 21, 22, 38) | B | B | R | B | B | B | B | B | B | B | B | B |
| Fusiform | B | B | R | B | B | B | B | B | B | B | B | B |
| Prietal pole/Wernicke’s area (BA 39, 40) | B | B | R | B | B | B | B | B | B | B | B | B |
| Inferior parietal, supramarginal gyrus (BA 39, 40) | B | B | R | B | B | B | B | B | B | B | B | B |
| Visual association gyrus (BA 17, 18, 19) | B | B | R | B | B | B | B | B | B | B | B | B |
| Anterior entorhinal cortex (BA 34) | B | B | R | B | B | B | B | B | B | B | B | B |
| Hippocampus | B | B | R | B | B | B | B | B | B | B | B | B |
| Parahippocampal gyrus | B | B | R | B | B | B | B | B | B | B | B | B |
| Ventral tegmental area | B | B | R | B | B | B | B | B | B | B | B | B |
| Raphé nuclei | B | B | R | B | B | B | B | B | B | B | B | B |
| Red nucleus | B | B | R | B | B | B | B | B | B | B | B | B |
| PAG | B | B | R | B | B | B | B | B | B | B | B | B |
| Substantia nigra | B | B | R | B | B | B | B | B | B | B | B | B |
| Claustrum | B | B | R | B | B | B | B | B | B | B | B | B |
| Amygdala | B | B | R | B | B | B | B | B | B | B | B | B |
| Brain stem | B | B | R | B | B | B | B | B | B | B | B | B |
| Lentiform nucleus | B | B | R | B | B | B | B | B | B | B | B | B |
| Pons | B | B | R | B | B | B | B | B | B | B | B | B |

(Calculated)
| Region                                      | Parts of which matrix |
|---------------------------------------------|------------------------|
| Primary somatosensory cortex (BA 1, 2, 3)   | Primary somatosensory cortex (BA 1, 2, 3) |
| Supplementary motor cortex (BA 6)           | Supplementary motor cortex (BA 6) |
| Motor cortex (BA 4, 4d)                     | Motor cortex (BA 4, 4d) |
| Visual association cortex (BA 17, 18, 19)   | Visual association cortex (BA 17, 18, 19) |
| Ventral tegmental area (VTA)                | Ventral tegmental area (VTA) |
| Raphé nucleus                               | Raphé nucleus |
| Substantia nigra                            | Substantia nigra |
| Midbrain                                    | Midbrain |
| Amygdala                                    | Amygdala |
| Brainstem                                   | Brainstem |
| Lentiform nucleus                           | Lentiform nucleus |
| Pons                                        | Pons |
| Basal ganglia                               | Basal ganglia |
| Palaeocortex (BA 40, 43)                   | Palaeocortex (BA 40, 43) |
| Thalamus                                    | Thalamus |
| Primary sensory cortex (BA 1, 2, 3)         | Primary sensory cortex (BA 1, 2, 3) |
| Hippocampus                                 | Hippocampus |
| Posterior cingulate cortex (BA 23, 31)      | Posterior cingulate cortex (BA 23, 31) |
| Anterior cingulate cortex (BA 24, 32, 33)   | Anterior cingulate cortex (BA 24, 32, 33) |
| Caudate                                     | Caudate |
| PAG                                         | PAG |
| Basal ganglia                               | Basal ganglia |
| Putamen                                      | Putamen |
| Posterior parietal cortex (BA 21, 39, 40)   | Posterior parietal cortex (BA 21, 39, 40) |
| Frontal pole/parietal cortex (BA 39, 40)    | Frontal pole/parietal cortex (BA 39, 40) |
| Inferior parietal, supramarginal gyrus (BA 1, 2, 3) | Inferior parietal, supramarginal gyrus (BA 1, 2, 3) |
| Temporal pole/primary auditory cortex (BA 21, 38) | Temporal pole/primary auditory cortex (BA 21, 38) |
| Frontal poles/parietal cortex (BA 39, 40)   | Frontal poles/parietal cortex (BA 39, 40) |
| Superior parietal cortex (BA 21, 38)        | Superior parietal cortex (BA 21, 38) |
| Inferior parietal, supramarginal gyrus (BA 1, 2, 3) | Inferior parietal, supramarginal gyrus (BA 1, 2, 3) |
| Temporal pole/primary auditory cortex (BA 21, 38) | Temporal pole/primary auditory cortex (BA 21, 38) |
| Frontal poles/parietal cortex (BA 39, 40)   | Frontal poles/parietal cortex (BA 39, 40) |
| Superior parietal cortex (BA 21, 38)        | Superior parietal cortex (BA 21, 38) |

When only the peak locations were reported the sprout022 tool (Dept. of Radiology and Biomedical Imaging, Yale School of Medicine) was used to identify the region.

If laterality applicable: B, Bilateral; C, Contralateral to stimulus; I, Ipsilateral to stimulus. If laterality not applicable: B, Bilateral; L, Left; R, Right.
The itch matrix categorized into three itch matrixes. First itch matrix consisted of primary and secondary somatosensory cortex (SI and SII, respectively), the parietal/central operculum, and the posterior insular cortex (pIC) (here presented in brown, this matrix is also presented in Figure 2A). The second itch matrix consisting of anterior singular cortex (ACC), anterior part of the middle cingulate cortex (aMCC), anterior part of the insular cortex (aIC), amygdala, striatum and hippocampus (here presented in blue, this matrix is also presented in Figure 2B). The third matrix contains prefrontal cortex, posterior part of the middle cingulate cortex (pMCC), and posterior cingulate cortex (PCC) (here presented in red, this matrix is also presented in Figure 2C).

involved with motivation aspects of itch and/or the carving for scratching.

According to original paradigms, two other studies have reported diminished activation of these regions in tasks that change the nature of pain perception with context variations (66) or with analgesia induced by meditation (67). While the first of these shows a diminished activation in dorsal ACC and insula as the subjects switch their perception from unpleasant to pleasant (or less unpleasant) revealing the link between emotional and motivational function. The second demonstrate that experienced Zen meditators can reduce activity of their prefrontal medial cortex, amygdala and hippocampus regions at the expense of an increased activity in dorsal ACC or insula which still belong to this second matrix but are more related to mindfulness. These articles suggest that making things more conscious by bringing activities closer to the awareness matrix (with insula as a common region) putatively lead to less harmful psychological consequences. This second matrix is more robust than the first one. Many arguments in the itch literature exist and converge about its functional role.

THIRD ITCH MATRIX

The third itch matrix would include parts of the prefrontal cortex, pMCC, and PCC (Figure 2C). This network should be involved in the subjective perception of itch. The cognitive state of the mind can affect the itch sensation e.g., emotions, obsessions, religious beliefs, disgusts, expectations, and past experiences. This pattern of activation is also present in the distraction from itch caused by the Stroop task (e.g., in the DLPFC) (14, 30, 34). The third matrix receives and integrates information from the foregoing two and triggers behavioral response.

CONCLUSION

Knowledge of itch processing in the brain is growing thanks to brain imaging (2, 68). A better understanding of interactions between itch matrixes would allow a better understanding
FIGURE 2 | Proposals for itch matrixes (X,Y,Z denotes the location of the corresponding slice in Montreal Neurological Institute (MNI) coordinate system). (A) Elements of the first matrix contributing to encoding of the recognition, localization, and intensity of itch. Primary sensorimotor cortex is presented in Blue, parietal operculum in Green, and posterior insular cortex in Red (Regions have been extracted from Automated Anatomical Labeling and Harvard-Oxford atlases). (B) The second matrix itch processing matrix consenting of anterior cingulate cortex (Blue), anterior insular cortex (Red), amygdala (Green) and hippocampus (Violet). This matrix is in charge of affective and motivational aspects of itch. (C) The third matrix consists of frontal cortex (Blue), middle cingulate cortex (Red), and posterior cingulate cortex (Green), and it is involved in the interpretation of the cognitive meaning of itch.

of pruritus in different cutaneous or extra-cutaneous etiologies (69).

AUTHOR CONTRIBUTIONS

LM, J-LC, DB, and OD contributed to conception and design of the study. PN organized the database and wrote the first draft of the manuscript. OD wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

ACKNOWLEDGMENTS

We thank the French Society of Dermatology for providing a grant.
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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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