Central mechanisms of itch: A systematic literature review and meta-analysis

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Abstract

In recent years, studying the central mechanism of itch has gained momentum. However, a proper meta-analysis has not been conducted in this domain. In this study, we tried to respond to this need. A systematic search and a meta-analysis were carried out to estimate the central mechanism of itch. The itch matrix comprises the thalamus and the parietal, secondary somatosensory, insular and cingulate cortices. We have shown that the basal ganglia (BG) play an important role in itch reduction. Finally, we explored itch processing in AD patients and observed that the itch matrix in these patients was different. In conclusion, this is the first meta-analysis on the central mechanisms of itch perception and processing. Our study demonstrated that different modalities of itch induction can produce a common pattern of activity in the brain and provided further insights into understanding the underlying nature of itch central perception.

1) Introduction

Itch is defined as an unpleasant sensation that prompts the urge to scratch [1,2]. Itch is the most frequent symptom of dermatological diseases, but it is not exclusive to these diseases, as a plethora of other diseases can generate this unpleasant sensation [3]. Itch is very commonly experienced; almost one-third of the global population suffers from itch in a given week [4,5]. It can dramatically reduce quality of life and can cause mental distress [6], including the occurrence of suicidal ideation [7]. Itch can be studied by two major approaches: one focuses on the skin and the peripheral nervous system (bottom-up approach), while the other focuses on the central mechanisms and how our brain perceives itch (top-down approach). Most itch studies have focused on the first approach. However, there have been some studies on the central mechanisms of itch in the last few years.

The closest phenomenon to itch is pain, and the degree of similarity between these two sensations is such that itch was considered a consequence of the low-level activation of nociceptors in the past [8]. It is now well known that increased itch will not cause pain and that itch is usually related to the activation of pruriceptors, followed by processing along a specific pathway from the skin to the brain [9–11]. The differences and similarities between pain and itch are apparent in the brain, as well [12].

Compared to pain, the central mechanisms of itch have been understudied. Nonetheless, a few studies have been performed, and a proper meta-analysis could be very helpful for reaching a consensus on the central mechanisms of itch. We performed a literature review and selected a handful of studies for this purpose; then, we used a specialized functional magnetic resonance imaging (fMRI) meta-analysis tool to extract the regions involved in itch processing.

We had four questions: Which regions of the brain are activated by itch induction? Which regions of the brain are correlated with itch intensity? Which regions are activated during itch inhibition? How can diseases affect the itch processing network in the brain? Therefore, we defined four clusters of studies – one for each question.

2) Materials and methods

2.1) Screening and eligibility cheek

To find all the relevant studies regarding neuroimaging and itch, a systematic literature search was performed through PubMed, Scopus and Web of Science in July 2019. We choose the key words to be as inclusive as possible. For PubMed, we used (("Magnetic Resonance Imaging"[Mesh] OR "Magnetoencephalography"[Mesh] OR "Spectroscopy, Near-Infrared"[Mesh] OR "Neuroimaging"[Mesh] OR "Electroencephalography"[Mesh] OR "Positron-Emission Tomography"[Mesh]) AND ("Pruritus"[Mesh])). For Scopus, the following keywords were used: TITLE-ABS-KEY ((itch OR pruritus) AND (EEG OR fMRI OR NIRS OR neuroimaging)) AND ((EXCLUDE (DOCTYPE, "re")). We used a flowing key word in the Web of Science, TS=(((itch) OR (pruritus)) AND ((((EEG) OR (fMRI)) OR (NIRS)) OR (MEG)) OR (neuroimaging))).

2.2) Inclusion criteria

Inclusion criteria were selected in a manner to be as inclusive as possible. There were three general inclusion criteria and a specific inclusion criterion for each question. The general inclusion criteria were as follows: 1) original research papers that used neuroimaging techniques to study the central

mechanisms of itch, 2) included a healthy group, 3) reported the coordination of the regions of interest (i.e., for EEG, NIRST, and MEG studies, this meant source localization was performed), and 4) conducted correlation or subtraction analysis (this meant that, unfortunately, all the connectivity analyses were excluded).

An additional criterion for the first group (subtraction analysis) was that the study should have compared data before and after itch induction. For the second group (correlation analysis), the additional criterion was that the study examined regions that correlated with itch levels. Another group included studies that employed an itch reduction method and reported the results (itch reduction group). Finally, for the chronic itch group, in the second inclusion criterion, the word "healthy" was replaced with "atopic dermatitis" (AD).

2.3) Meta-analysis

Meta-analysis was carried out using the anisotropic effect size version of signed differential mapping (AES-SDM) software, version 5.15 (www.sdmproject.com), which has been validated and used for several structural and functional fMRI studies [13]. This software created a brain map of the effect size of the brain activity for each study (for the statistical maps and the peak value information); then, it would conduct a meta-analysis in a voxel-wise random effects manner (calculating study weights based on sample size and variance) [14]. Based on the Radua & Mataix-Cols study [15,16], SDM parameters were set as follows: 100% for anisotropy and 25 for kernel full width at half maximum with 100 Monte Carlo permutations. Finally, the voxel threshold was set to $P<0.005$, while the peak height threshold was set as SDM-Z>1, and the extend threshold was set as a cluster size≥10 voxels.

3) Results

3.1) Included studies

Searches in PubMed, Web of Science, and Scopus yielded 127, 84, and 194 papers, respectively. After pooling all the papers together, 314 papers were identified, and 3 additional papers that were not found with this process were added to the pool [17–19]. After reading their titles and abstracts, 270 papers were eliminated in the screening stage. Finally, 47 papers were selected for full text examination. A detailed description of these procedures is presented in the PRISMA flowchart shown in Figure 1. (A table containing these papers is presented in Table 1). The papers that were excluded after full text examination and the reason for their exclusion are presented in Table S1.

After examining all the studies, 16 were included in the subtraction-based group. In the correlation group, 6 studies were included. The inclusion criteria resulted in 6 studies being included in the itch reduction group. Finally, 5 were included in the AD section.

In the next stage we test for assumptions that needed to be true in order for spatial convergence to be valid. We have used the method described by Albajes-Eizagirre and Radua [20]. Pooling of the original subtraction based studies resulted in the fact that meta-analysis had a maximum of 8 while the threshold was 5. This meant that the subtraction based studied retained the spatial convergence assumptions. The original correlation based studies resulted in a maximum of 5 while the threshold was 3, meaning that it upholds the assumptions too. The itch reduction studies had a similar result with a maximum for the original meta-analysis of 5 while the threshold was 4. Finally, in the AD studies the original meta-analysis had maximum value of 4 while the threshold was 3. These meant that all four of

the meta-analysis retained the spatial convergence assumptions. A detailed method and results of these tests is presented in supplementary data section S3.

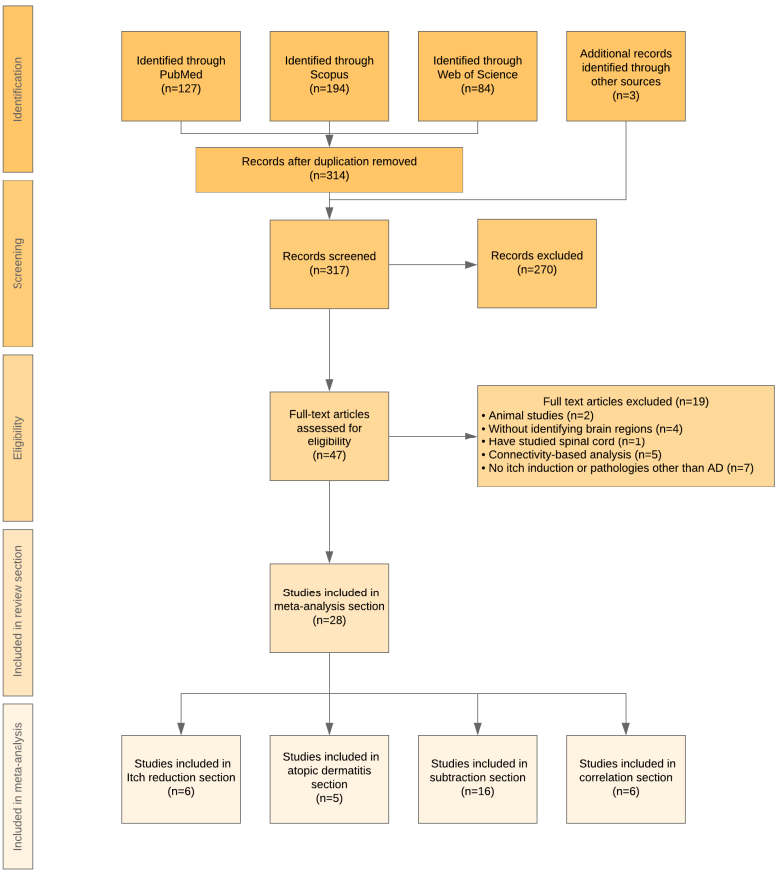

Figure 1: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart of meta-analysis

Table 1: All the papers that were included and the group in which they were included. Some papers were included in more than one group (they reported multiple results that satisfied our inclusion criteria).

Groups	*Studies*	*Number of subjects*
Subtraction	(Bergeret et al., 2011) [21]	14
	(Darsow et al., 2000) [18]	6
	(Holle et al., 2012) [22]	18
	(Hsieh et al., 1994) [17]	28
	(Ishiuji et al., 2009) [23]	7
	(Leknes et al., 2007) [24]	8
	(Mochizuki et al., 2013) [12]	18
	(Mochizuki et al., 2019) [25]	25
	(Mochizuki et al., 2009) [26]	10
	(Mochizuki et al., 2007) [27]	14

	(Mochizuki et al., 2014) [28]	16
	(Mochizuki et al., 2003) [29]	15
	(Papoiu et al., 2012) [30]	15
	(Schneider et al., 2008) [31]	6
	(Valet et al., 2007) [32]	12
	(van de Sand et al., 2018) [33]	30
Correlation	(Bergeret et al., 2011) [21]	14
	(Drzezga et al., 2001) [19]	6
	(Herde et al., 2007) [34]	10
	(Kleyn et al., 2012) [35]	16
	(Mochizuki et al., 2007) [27]	14
	(Walter et al., 2005) [36]	6
Reduction	(Mochizuki et al., 2015) [37]	10
	(Mochizuki et al., 2014) [28]	16
	(Papoiu et al., 2015) [38]	24
	(Papoiu et al., 2013) [39]	14
	(Stumpf et al., 2017) [40]	33
	(Vierow et al., 2009) [41]	15
Atopic dermatitis	(Ishiuji et al., 2009) [23]	8
	(Napadow et al., 2015) [42]	14
	(Napadow et al., 2014) [43]	14
	(Schneider et al., 2008) [31]	8
	(Schut et al., 2017) [44]	11

3.2) Subtraction-based studies (itch matrix)

Figure 2 shows the results of the meta-analysis for the studies that used subtraction to report itch-induced brain activity. Locations of the peak and Z values of these regions are presented in Table 2. Six clusters were identified:

1) Right insular cortex expanding into the Rolandic operculum, frontal operculum, superior temporal gyrus, and lenticular nucleus (putamen);
2) Same area as 1, but in the left hemisphere;
3) Bilateral supplementary motor area expanding into the middle and anterior cingulate cortex and medial superior frontal gyrus;
4) Bilateral thalamus with parts expanding into the caudate nucleus;
5) Right inferior parietal gyri expanding into the angular gyrus and supramarginal gyrus; and
6) Left supramarginal gyrus.

Table 2: Location of the peaks in each cluster of the meta-analysis. Blobs of ≥ 25 voxels with all voxels SDM-Z ≥ 2.565 and all peaks SDM-Z ≥ 2.674

#	*MNI coordinate*	*SDM-Z*	*p*	Voxels	Description
1	48,10,8	5.145	~0	5068	Right insula, BA 48
2	-42,16,0	4.322	0.000001	4589	Left insula, BA 48
3	0,22,36	4.094	0.000002	4010	Left median cingulate / paracingulate gyri, BA 24
4	-6,-6,4	4.286	0.000001	1021	Left thalamus
5	54,-50,36	3.1	0.000378	505	Right angular gyrus, BA 40
6	-60,-26,28	2.674	0.003047	25	Left supramarginal gyrus, BA 48

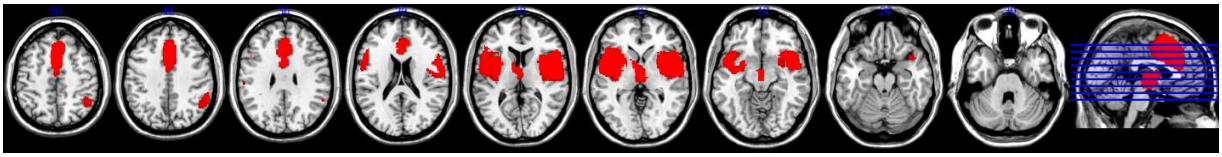

Figure 2: Meta-analysis results for the central mechanism of itch perception

3.3) Itch correlation

In another section of the meta-analysis, the idea that the activity of some brain regions could be correlated with itch intensity was explored. This analysis found six regions correlated with itch intensity, of which four regions had a positive correlation and two regions had a negative correlation; shown in Figure 3. The peak locations and the P values of these clusters are presented in Table 3. Regions with a positive correlation with itch intensity consisted of the following:

1) This cluster was similar to cluster 1 in the itch subtraction analysis. Left insular cortex expanding into the left cortex, inferior frontal gyrus (triangular and opercular parts), and superior temporal gyrus.
2) Bilateral middle cingulate cortex expanding into the bilateral cingulate cortex and bilateral supplementary motor area (the left SMA was more applicate). This cluster was more prominent in the right hemisphere of the brain.
3) This cluster was effectively the right counterpart of cluster 1. It consisted of the right insula, right Rolandic operculum, and inferior frontal gyrus.
4) The fourth cluster was mostly situated in the left caudate nucleus.

The clusters that had a negative correlation with itch intensity were as follows:

1) Left fusiform and parahippocampal gyri extending into the left inferior temporal gyrus.
2) Bilateral anterior cingulate cortex.

Table 3: Regions whose activity correlated with itch intensity. Blobs of ≥ 303 voxels with all voxels SDM-Z ≥ 1.686 and all peaks SDM-Z ≥ 2.213 for positive correlation and blobs of ≥ 270 voxels with all voxels SDM-Z ≤ -0.791 and all peaks SDM-Z ≤ -1.099 for negative correlation

	#	*MNI coordinate*	*SDM-Z*	*p*	Voxels	Description
Positive Correlation	1	-48,20,10	2.899	0.000003	2097	Left inferior frontal gyrus, triangular part, BA 45
	2	8,26,38	2.78	0.000005	2025	Right median cingulate / paracingulate gyri, BA 32
	3	42,12,-2	2.213	0.000187	1727	Right insula, BA 48
	4	-12,2,18	2.293	0.000111	303	Left caudate nucleus
Negative correlation	1	-32,-4,-32	-1.559	0.000012	958	Left fusiform gyrus, BA 36
	2	6,38,-2	-1.099	0.000587	270	Right anterior cingulate / paracingulate gyri, BA 11

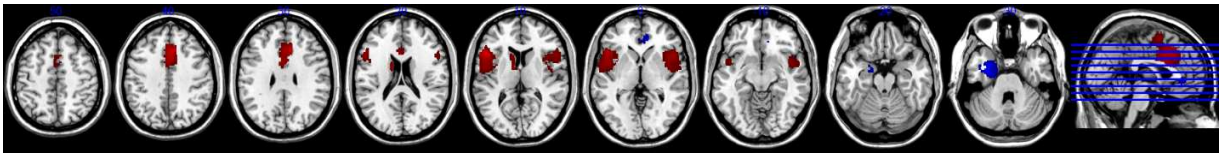

Figure 3: Meta-analysis result for brain regions whose activity was correlated with itch intensity

3.4) Reduction

Eight brain regions showed changes in activity after itch reduction, and they are presented in Table 4 and Figure 4:

1) Right insular cortex and right Rolandic operculum expanding into the superior temporal gyrus and Heschl's gyrus, including considerable contributions in the right lenticular nucleus (putamen) and right striatum;
2) Left insular cortex expanding into left lenticular nucleus (putamen) and left striatum;
3) Left thalamus;
4) Bilateral middle and anterior cingulate cortex;
5) Left precentral and inferior frontal gyri;
6) Right precentral gyrus;
7) Right thalamus; and
8) Left cerebellum (crus I), with small parts extending into the fusiform gyrus.

Table 4: Peak location of all the clusters in the studies showing reduction in itch levels after meta-analysis. Blobs of ≥ 39 voxels with all voxels SDM-Z ≥ 2.308 and all peaks SDM-Z ≥ 2.408

#	*MNI coordinate*	*SDM-Z*	*p*	Voxels	Description
1	30,0,12	3.761	0.000011	4305	Right lenticular nucleus, putamen, BA 48
2	-16,-2,-6	4.043	0.000004	999	Left striatum
3	-16,-22,12	3.397	0.000047	468	Left thalamus
4	-2,24,34	2.835	0.000424	438	Left median cingulate / paracingulate gyri, BA 24
5	-42,2,36	2.731	0.000706	372	Left precentral gyrus, BA 6
6	48,-10,42	2.93	0.000290	220	Right precentral gyrus, BA 4
7	16,-22,6	2.512	0.002071	42	Right thalamus
8	-24,-78,-18	2.408	0.002071	39	Left fusiform gyrus, BA 18

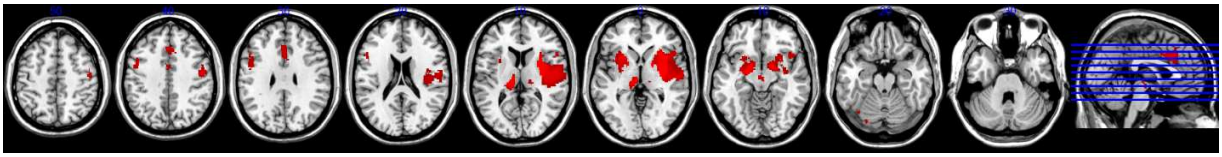

Figure 4: Result of the reduction meta-analysis

3.5) Atopic dermatitis

The meta-analysis showed six clusters that have been shown to be activated by itch in AD patients. There regions are presented in Figure 5 and Table 5:

1) Left striatum, lenticular nucleus (putamen), caudate nucleus and parts expanding into the insula;
2) Right middle frontal gyrus (Brodmann areas 9, 8, and 46);

3) Right caudate nucleus;
4) Right lenticular nucleus (putamen) and right striatum;
5) Bilateral anterior cingulate gyri; and
6) Left superior frontal gyrus and left supplementary motor area.

Table 5: Peak location and the Z value of all the significant clusters from the meta-analysis on itch perception in AD patients. Blobs of ≥ 23 voxels with all voxels SDM-Z ≥ 1.564 and all peaks SDM-Z ≥ 1.651

#	*MNI coordinate*	*SDM-Z*	*p*	Voxels	Description
1	-26,8,-4	2.242	0.000186	1084	Left lenticular nucleus, putamen, BA 48
2	36,26,46	3.382	0.000003	814	Right middle frontal gyrus, BA 9
3	14,12,14	2.918	0.000011	494	Right caudate nucleus
4	26,4,-10	1.651	0.003488	110	Right lenticular nucleus, putamen, BA 48
5	6,18,22	1.999	0.000636	59	Right anterior cingulate / paracingulate gyri
6	-4,26,46	1.673	0.003189	23	Left superior frontal gyrus, medial, BA 8

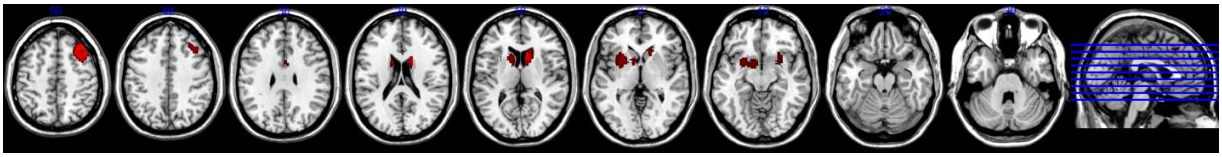

Figure 5: The itch processing network in AD patients

4) Discussion

Image-based meta-analysis (IBMA) are gold standard for fMRI meta-analysis, but their use is limited because they need statistical maps of all the studies, which normally are not publicly available. Therefore, most studies use coordinate-based meta-analysis (CBMA). Among CBMA based methods effect size signed differential mapping (ES-SDM) combines the advantages of other methods while improving upon them by adding features like effect size and polarity of the peaks, furthermore anisotropic ES-SDM (AES-SDM) uses anisotropic kernels to reduces ES-SDM's dependency on Full width at half maximum (FWHM) [13]. A more comprehensive explanation of these methods is presented in the supplementary material and methods (S2).

Hence, the central mechanism of itch perception involves many brain areas. In this meta-analysis, we provide a validated synthesis of these areas.

After the transmission of the itch signal to the brain, the thalamus dispatches it into the principal itch matrix. The reason that we call this network the itch matrix is that, similar to its counterpart "pain", there is no one region that specifically encodes itch. We briefly explore the important elements of this itch matrix. Primary somatosensory cortex (SI) and secondary somatosensory cortex (SII) are among the regions that are activated during most itch stimuli [19,38,45,46]. In pain studies, these regions play crucial roles in the encoding of the location and intensity of pain [47,48]. Based on pain studies [49–51], some researchers suggest that activity in the SI has a linear relationship with itch intensity and that the activity in the SII has a sigmoid (S-shape function) relationship with itch intensity [52]. Another region that plays an important role in itch processing is the motor cortex (including but not limited to supplementary motor area (SMA), premotor cortex (PM) and primary motor cortex (MI)), which is especially important in scratching. We should mention that in most studies, subjects' movements were

restricted and the subjects were not allowed to scratch; even with these restrictions, some studies have observed activation in motor regions [23,33,44,53]. This result occurred because even imagining an action can activate the motor cortex in anticipation of it [54,55]. Another region involved in itch perception is the insular cortex (IC), which is divided into two parts: the posterior and anterior insula. The posterior insular cortex (pIC) receives sensory signals through the spinothalamic tract (STT) [56]; therefore, as with pain [57], its activity is one of the earliest in conscious nociception and pruriception. Unlike the pIC, the anterior insular cortex (aIC) has been shown to be involved in subjective itch sensation, the unpleasantness of itch and the regulation of the amount of attentional resources allocated to itch [57,34,24,27,58,30]. The cingulate cortex is divided into three main regions: the anterior cingulate cortex (ACC), midcingulate cortex (MCC), and posterior cingulate cortex (PCC). It is generally accepted that, in the pain matrix, the ACC is involved in the affective experience of the pain, while the MCC and PCC are responsible for the cognitive aspects of pain [48,57]. In itch studies, all three of these regions have been reported to be involved, though references to the ACC and MCC seem to be more prevalent [28,35,37,46,59]. It is believed that the cingulate cortex is involved in the cognition or evaluation of itch or perhaps in the urge to scratch [58].

Before any further discussion of the studies, we should mention some limitations. SDM estimates the statistical maps based on their peak reported in the papers; therefore, a statistical map of two peaks in proximity could interfere with each other. The fact that some regions are clustered together does not always indicate that they are activated together. Finally, the regions reported here are not all the regions involved in the itch matrix, and some regions could have been excluded due to inter-study inhomogeneities.

In the meta-analysis of the itch matrix, our goal was to study the base matrix that is involved in itch perception. Our results showed two bilaterally symmetrical clusters in the insular and Rolandic operculum (SII); these results were expected because most studies report itch-induced activity in these regions. Another cluster was the bilateral SMA, which expanded into the middle and anterior cingulate cortex; as we mentioned before, this cluster is probably involved in the emotional aspects of itch perception (cognition and affective aspects). Finally, the activation in the thalamus was also expected because it is probably the region that dispatches itch information to other brain regions. However, the activation pattern lacks two regions that are believed to play important roles in itch perception, namely, SI and MI. Their absence could be due to some inhomogeneity in the studies, as we have included so many studies with many different itch induction modalities. This result could also be due to the somatotopic organization of SI responses to itchy stimuli. It has already been shown that the SI response to pain is organized in a somatotopic manner [47]; it is possible that itch has the same organization, as well. Finally, the activity of these missing regions could have been mixed with other parietal regions, and the response is included in their significance. Alternatively, simply the number of studies reporting the activity of these regions is too small, which resulted in a small SDM-Z value that did not survive the thresholding.

An interesting finding in this section was the activity of the right angular gyrus. The angular gyrus has been reported to be involved in higher aspects of motor control, e.g., predicting movement consequences and goal-directed movements [60,61]. The activation of this region could be the first link in the chain reaction that results in scratching (a goal-directed movement). The angular gyrus is also part of the default mode network [62] and plays an important role in the attention regulation [63,64], which

means that it could play a role in reorienting attention towards itch. Another possible role of this region is that it is involved with the spatial cognition of itch [65].

In the correlation study, we examined whether a network of brain regions exists whose activity correlates with itch intensity. The resulting clusters are presented in Table 3. Although the peak of cluster 1 is in the inferior frontal gyrus, the majority of the cluster is in the insular and operculum cortices. Clusters 1, 2, and 3 in the correlation analysis are similar to clusters 1, 2 and 3 in the subtraction analysis, respectively. The fourth cluster is the left caudate nucleus. Together, the caudate and the putamen constitute the striatum, which, in turn, is a component of the basal ganglia (BG). The striatum is part of the dopaminergic motor system and is involved in cognitive, motor and emotional activities [66]. The involvement of the BG in pain processing is supported by both clinical and preclinical data [66–68]. The results of our meta-analysis support the fact that the BG also plays an important role in itch processing. The BG is a region known for multisensory integration [69,70]. Therefore, its involvement in itch perception, which has both sensory and motor (scratching) aspects, is not surprising. In pain studies, the activation of the caudate has been associated with the pain modulatory system [71,72]. The caudate could also be involved in the reduction of the affective components of pain [66]. We believe that the caudate is similarly involved in affective aspects of itch and helps its modulation. The activation of the putamen was also believed to be involved with the motor aspect of the pain[73,74], but recent studies suggest that the putamen is involved in other aspects of pain [75]. Starr et al. [75] reported that pain sensitivity decreased in patients with putamen lesions. Similarly, the putamen probably plays a role in itch processing both in the sensation and motor (scratching) aspects of it. Though reporting itch-induced activity in the temporal pole is not uncommon, the activity reported in cluster 1N of the correlation analysis is possibly due to activation in the parahippocampal gyrus, considering that almost half of this cluster is in the parahippocampal gyrus. Interestingly, the pain response in the parahippocampal gyrus was positively correlated with pain intensity [76].

The results of our meta-analysis on itch reduction studies confirm that the basal ganglia plays an important role in itch reduction. Much of clusters 1 and 2 in the itch reduction analysis is situated in the BG, though these clusters also had considerable contribution in the insular cortex. Activity in cluster 4, comprising the bilateral middle and anterior cingulate cortex, is thought to reflect the cognitive response. These regions are believed to play a role in itch cognition and the desire to scratch. The activation of this cluster during itch reduction could have been caused by the relief from the itch or the motor aspect of scratching, having nothing to do with itch relief. The same argument can be made for clusters 5 and 6: the primary motor cortex and supplementary motor area. It is uncertain whether the activity in the motor cortex is due to scratching or another reason. However, a study[40] that deployed distraction for itch reduction showed higher activation in these regions during the Stroop task with histamine-induced itch.

The meta-analysis of itch processing in AD patients shows vast differences in itch-induced activity. Clusters 1, 3, and 4 were clusters in the AD meta-analysis that were part of the BG. Unlike the BG clusters in the correlation or itch reduction analyses, these clusters did not extend into the insular cortex or Rolandic operculum (or their extension was minimal). They also included regions in the frontal cortex (namely, Brodmann areas 8 and 9) involved in planning complex movements [77] (possibly scratching) or emotional senses [78] (distinguishing whether a sensation or emotion is pleasant or not). The increased activation of the BG in these patients could be due to the itch-scratch cycle, and the fact that patients

tend to scratch themselves more often and, therefore, reinforce these activities in the BG, as part of the dopaminergic motor system.

Among itchy diseases, AD was chosen because it was the only disease on which more than 3 studies had been performed.

In conclusion, this is the first meta-analysis on the central mechanisms of itch perception and processing. We explored the principal itch matrix by performing a meta-analysis on subtraction-based studies and correlation-based analysis. This itch matrix comprised SII, insular cortex, cingulate cortex, thalamus, and some regions in the parietal cortex. Then, we showed that the BG plays an important role in itch reduction and that itch reduction also activates the SMA and MI. Finally, we explored itch processing in AD patients and observed that the itch matrix in these patients was different.

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