Functional Magnetic Resonance Imaging and Applications in Dermatology

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As a noninvasive imaging modality able to show the dynamic changes in neurologic activity, functional magnetic resonance imaging has revolutionized the ability to both map and further understand the functional regions of the brain. Current applications range from neurosurgical planning to an enormous variety of investigational applications across many diverse specialties. The main purpose of this article is to provide a foundational understanding of how functional magnetic resonance imaging is being used in research by outlining the underlying basic science, specific methods, and direct investigational and clinical applications. In addition, the use of functional magnetic resonance imaging in current dermatological research, especially in relation to studies concerning the skin–brain axis, is explicitly addressed. This article also touches on the advantages and limitations concerning functional magnetic resonance imaging in comparison with other similar techniques.

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INTRODUCTION

With the introduction of a stimulus or the performance of a cognitive task, functional magnetic resonance imaging (fMRI) records data from the entire brain every few seconds, creating a time series of brain activity. The stimulated neurons require greater oxygenation, increasing cerebral blood flow to the activated regions of the brain and forming the physiological basis of the fMRI signal. fMRI has an advantage over other functional mapping techniques, such as electrical stimulation mapping, because it noninvasively establishes a relationship between localized brain activity and a particular function encompassing the entire brain.

The initial demonstration of magnetic resonance imaging's capability in linking anatomy with neurologic activity came when Ogawa et al. (1990) described the effect of blood oxygenation level–dependent (BOLD) contrast, an endogenous technique creating contrast, forming the basis for fMRI. These investigators showed that BOLD contrast could be used to monitor real-time blood oxygenation changes in the brain in response to CNS-modulating drugs that affect metabolism or blood flow (Ogawa et al., 1990). In the following years, the link between BOLD contrast and neurologic activity was established using visual stimulation (Kwong et al., 1992; Ogawa et al., 1992). Arterial spin labeling (ASL), an alternative method to measure blood flow by magnetically labeling blood before entering the brain, surfaced that same year. First developed in rat brains (Detre et al., 1992; Williams et al., 1992), ASL was soon used by Kwong et al. (1992) to help verify BOLD fMRI (Koretsky, 2012). Not until several years later would ASL be utilized independently for fMRI in human studies using visual stimulation similar to that used by Kwong et al. (1992) and Ogawa et al. (1992) (Talagala and Noll, 1998).

When compared with methods such as electroencephalography and magnetoencephalography, fMRI has a superior spatial resolution. Conversely, magnetoencephalography and electroencephalography provide superior temporal resolution on the order of milliseconds, and efforts have been made to make the modalities complementary (Hall et al., 2014) and to model and integrate their results (Babajani and Soltanian-Zadeh, 2006). Another method developed alongside fMRI is positron emission tomography. Although able to provide comparable images and conclusions, positron emission tomography requires the injection of radioactive agents, preventing a significant number of tests from being run over time (Kwong et al., 1992). Early attempts were made at using exogenous contrast agents in fMRI (Belliveau et al., 1991), but it fell out of favor compared with the noninvasive methods that quickly followed.

METHODS AND DESCRIPTION

Measuring neural activity: BOLD contrast and ASL

The fMRI signal behind BOLD contrast results from dynamic changes in blood flow, volume, and oxygenation in metabolically active tissues (Figure 1). When oxyhemoglobin releases oxygen, it transitions from diamagnetic to paramagnetic states, producing a difference in magnetic susceptibility between blood vessels, surrounding tissues, and the water molecules themselves. This deoxyhemoglobin effect dampens the magnetic resonance signal in that particular area of tissue (Ogawa et al., 1990). An increase in deoxyhemoglobin concentration will therefore be read as a decrease in

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Abbreviations: ASL, arterial spin labeling; BOLD, blood oxygenation level–dependent; fMRI, functional magnetic resonance imaging

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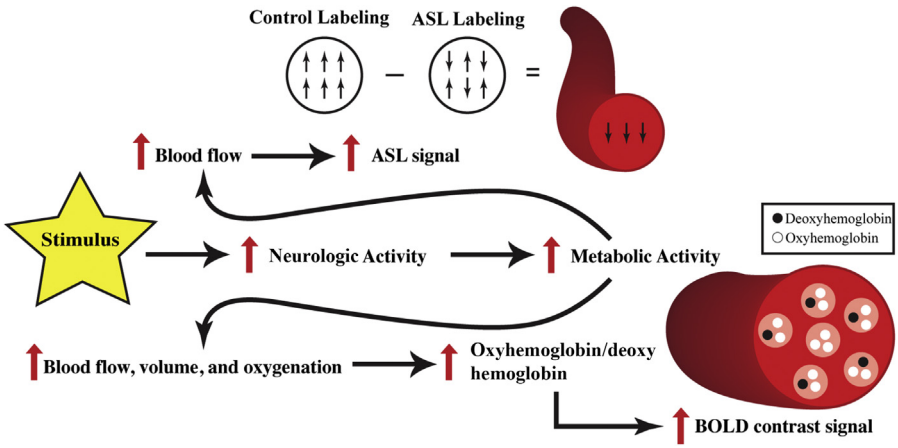

Figure 1. The physiological origins of the signals behind BOLD contrast and ASL fMRI. As noted in the top half of the figure, an increase in blood flow of labeled protons when compared with that of the control labeling will result in the activation signal shown in ASL. In the lower half, a combination of increased blood flow, volume, and oxygenation increases the ratio of oxyhemoglobin-to-deoxyhemoglobin providing the changes in BOLD contrast. ASL, arterial spin labeling; BOLD, blood oxygenation level–dependent; deoxy, deoxygenated; fMRI, functional magnetic resonance imaging.

image intensity, whereas a decrease in deoxyhemoglobin will show an increase in image intensity resulting in the different ratios of oxygenated to deoxygenated hemoglobin underlying BOLD contrast. Linking BOLD contrast to neural activity can be understood by the model of the hemodynamic response. This model suggests that increased neural activity results in an increase in brain metabolism, requiring more oxygen consumption and blood flow (Malonek et al., 1997). With neural activity, there is first a small decrease in image intensity during oxygen consumption and increasing concentration of deoxyhemoglobin, followed by a large increase in intensity due to increasing oxygenated blood flow and decreasing deoxyhemoglobin (Heeger and Ress, 2002). The BOLD contrast signal itself is primarily produced by macroscopic veins and venules (Lai et al., 1993). The brain regions active during a stimulus are determined by subtracting the difference of the average of the resting-state images.

Although similar to BOLD contrast, ASL is an fMRI technique measuring neurologic activity by cerebral perfusion within capillaries and arterioles with magnetically labeled blood water protons as the diffusible contrast media. Generally, inflowing protons are labeled externally at the neck by radiofrequency pulses before image acquisition in the brain as a part of ASL sequences that now can be performed using clinical magnetic resonance imaging scanners. Labeling can be characterized as either continuous ASL, pulsed ASL, or pseudocontinuous ASL by the duration and frequency of radiofrequency pulses. As the first method described, continuous ASL occurs by inverting these protons' spin with continuous 2–4 seconds of radiofrequency energy in the setting of a magnetic field in the direction of blood flow as shown in Figure 2 (Ferré et al., 2013; Williams et al., 1992). Improving on this method, pseudocontinuous ASL uses a rapid sequence of millisecond pulses, which offers superior labeling efficiency and is compatible with the standard hardware of modern magnetic resonance imaging scanners (Alsop et al., 2015). Further complexities associated with the variations in labeling techniques are not discussed in this paper. After labeling, these water molecules will subsequently perfuse the tissue of interest that is comparatively more metabolically active than the surrounding tissue. The decay time is long enough for the labeled blood's perfusion into microvasculature to be detected and short enough for alterations of interest to be recorded. This exchange of the labeled water protons within the activated distal tissues causes a change in the magnetic signal proportional to the increase in blood flow (Detre and Wang, 2002). The extent of this alteration can be quantified by pair-wise comparison with images acquired by control labeling that does not alter the magnetization of arterial water as shown in Figure 1 (Detre and Alsop, 1999).

Identifying brain regions with significant activities by fMRI requires extensive preprocessing and postprocessing. Individual results must be integrated across subjects using a neurologic atlas such as the Talairach or the Montreal Neurological Institute (Canada). For example, the Montreal Neurological Institute is a probabilistic map created by combining scans from over a hundred individuals. The final product displays a brain activation map illustrating the neurologic activity associated with that stimulus or task. This process incorporates quality control measures, including the assessment of patient head motion, functional anatomic alignment, susceptibility artifacts, and advanced statistical analysis (Gujar et al., 2017). Given the significant advances since the development of fMRI, image processing that had previously taken almost an entire day can be performed in under an hour.

Experimental design and methods

Keeping the foundational concepts underlying fMRI in mind, the next step is to understand the experimental methods used to link the particular neurologic activity of interest with brain anatomy and functionality. Task-based fMRI is the original method utilized in the early fMRI studies (Kwong et al., 1992; Ogawa et al., 1992), whereby the subject alternates between stimulated and resting states. Task-based fMRI can either be block design, which involves nonrandom time-specific sequential activation–rest paradigms, or can be event related, in which both the stimulus time and sequence are randomized. Whereas the block design has higher detection power and easier implementation for the investigator, the event-related design shows comparable activation patterns and has been suggested to overcome the confounding effects of anticipation associated with block design (Chee et al., 2003; Pilgrim et al., 2002).

BOLD versus ASL

Although comparable, certain advantages distinguish the two methods. ASL measures absolute perfusion values, allowing single values to be compared across subjects and enabling disease states to be measured against other pathologies or normal populations. BOLD is only able to measure relative values or percentage changes across different subjects. Changes in basic metabolism by drugs or particular disease states may alter the BOLD signal,

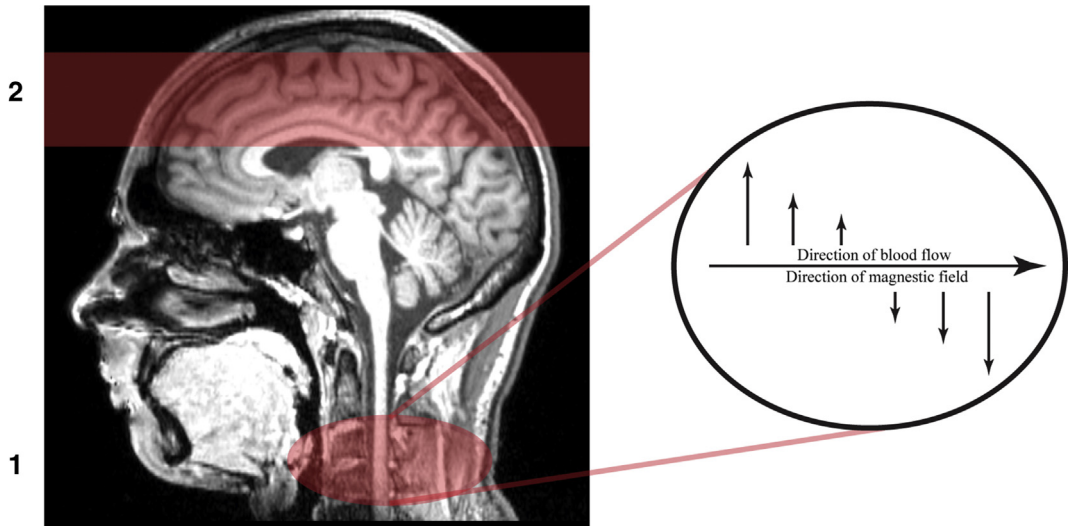

Figure 2. The labeling process is a preliminary step in the ASL functional imaging protocol occurring at point 1 before blood enters the tissue of interest where the functional images are acquired at point 2. At point 1, radiofrequency energy can either be applied continuously or in pulses with varying frequency differentiating CASL, PCASL, and PASL. The radiofrequency pulses are applied in tandem with a magnetic field gradient in the direction of blood flow, resulting in inversion of proton spin as shown (Ferré et al., 2013). This experiment is then repeated without tagging with the control image acquired at point 2. ASL, arterial spin labeling; CASL, continuous arterial spin labeling; PASL, pulsed arterial spin labeling; PCASL, pseudocontinuous arterial spin labeling.

making it difficult to compare with other populations. During an ASL imaging session, BOLD images are also able to be obtained for the study, providing more data than an isolated BOLD study (Federspiel et al., 2006). The subtraction methods of ASL are less susceptible to low-frequency noise in comparison with those of BOLD contrast, making it more desirable for slow, continuous changes in neural activity over the course of several minutes (Aguirre et al., 2002). BOLD contrast has superior temporal resolution and significantly higher sensitivity for detecting neurologic activity, making it more suitable for on-and-off, fast event-related experiments investigating complex processing and tasks (Federspiel et al., 2006). A comprehensive comparison between BOLD and ASL is provided in Table 1.

Functional connectivity

Beyond analyzing simple tasks and their isolated regions of neurologic activity, functional imaging has the ability to unravel complex networks of associated regions of brain activity forming a concept known as functional connectivity. An example of the brain network map regarding the differences in connections between patients with psoriasis and healthy controls is shown in Figure 3 (Najafi et al., 2020a). With roots in electrode experiments from the late 1960s, functional connectivity can be defined as temporal correlations between spatially remote neurophysiological events (Friston, 1994; Gerstein and Perkel, 1969). A different type of fMRI, resting-state fMRI, was first used by Biswal et al. in 1995 to further understand the functional networks of the human brain. In resting-state fMRI, low-frequency changes in the BOLD contrast signal are evaluated while the patient is at rest. A variety of brain networks have been studied using this methodology, with the default mode network receiving the most attention. Dysfunction in the default mode network has been described, providing a better understanding of a variety of neuropsychological disorders (Broyd et al., 2009). As shown in the later discussion, functional connectivity is not limited to resting-state fMRI experiments but can be applied to any neurophysiological event of interest.

DISCUSSION AND POTENTIAL APPLICATIONS

Applications in dermatology

Skin–brain axis. The skin and brain are connected from the very beginning of embryogenesis given their common embryonic layer. This connection is clearly demonstrated by the sensory homunculus of the postcentral gyrus representing the entire surface of the skin. These sensory inputs have widespread effects throughout the human body, including emotional, behavioral, endocrine, and immune functions. Early attempts using electroencephalography in the 1950s made efforts to uncover the functional connections of the skin–brain axis (Mueller et al., 2017). fMRI has proven to be a valuable investigative tool for exploring the sensory experiences associated with pain (Apkarian et al., 2005). Owing to

Table 1. Comparing fMRI Methods Based on BOLD Contrast and ASL

Characteristic	BOLD Contrast	ASL
Signal formation	Changes in blood flow, volume, and oxygenation	Blood flow
Sensitivity	High	Low
Nature of signal changes	Relative	Absolute
Spatial specificity	Venules and draining veins	Capillaries, arterioles
Temporal resolution	>1 s	>2 s
Task advantage	Complex	Continuous (itch)
Individual subject variability	High	Low
Major artifact	Motion, baseline drift	Vascular

Abbreviations: ASL, arterial spin labeling; BOLD, blood oxygenation level–dependent; fMRI, functional magnetic resonance imaging.
It is noteworthy that the information presented in this table is pooled from Detre and Wang (2002) and Federspiel et al. (2006).

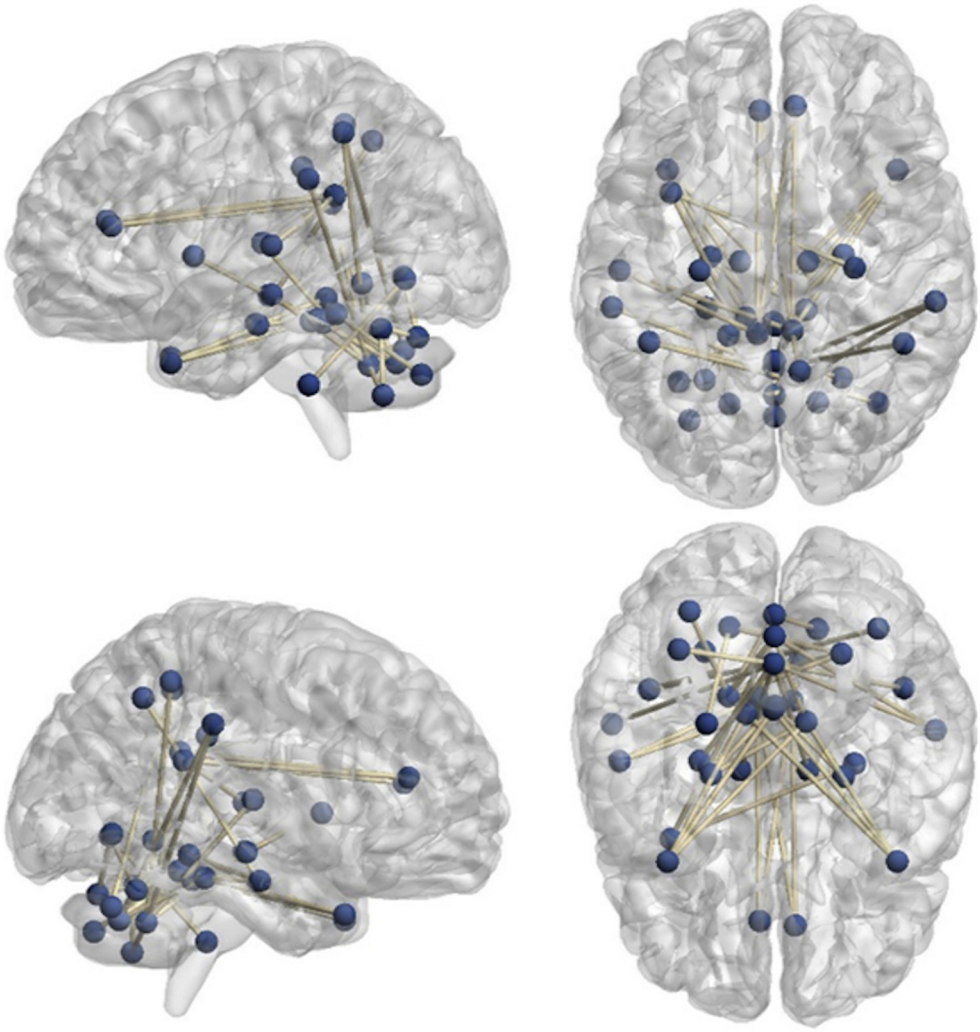

Figure 3. The brain networks that have significantly different connections between patients with psoriasis and healthy controls. (Reprinted from Najafi et al., 2020a with permission from John Wiley & Sons).

the complex and overlapping relationship between pain and pruritus, these early studies focusing on pain were able to lay the foundation for similar analysis to be applied to other pathological manifestations of the skin–brain axis, with an obvious initial focus on pruritic pathologies (Najafi et al., 2021a).

A deeper understanding of pruritus. Most previous fMRI studies in dermatological research have focused on the neuroanatomical maps related to pruritus, defined as an uncomfortable sensation on the skin causing the desire to scratch. In relation to pruritus, the ultimate goal of fMRI is to uncover a deeper understanding of the itch–scratch response and to determine which areas of the brain are involved. With particular regions identified, the next steps include forming functional maps of these regions with hopes of better understanding the targets for intervention.

Early functional imaging studies concerning pruritus utilized positron emission tomography, with the first BOLD contrast imaging study surfacing in 2005 (Walter et al., 2005). The early BOLD contrast studies were limited by the short duration of the BOLD signal for studying the extended duration of the itch sensation and the brain response. The advantages of ASL over BOLD contrast in studying slower changes in brain activity make it the ideal imaging technique for studying pruritus (Papoiu, 2016).

The first pruritus-related study utilizing ASL, reported in 2009 (Ishiuji et al., 2009), established that histamine-induced pruritus showed differences in brain activation patterns between patients with chronic pruritus with atopic dermatitis and healthy subjects. In addition, affected areas could be correlated with disease severity. Many studies utilizing ASL followed seeking to refine the functional maps concerning pruritus and to describe other pruritic conditions.

fMRI has been able to differentiate the areas of the brain responding to different pruritic mediators, including histamine and cowhage (Papoiu et al., 2012), ultimately leading to a study showing the differences in efficacy between pharmacologic therapy (Papoiu et al., 2015). Papoiu et al. (2015) showed complete suppression of histamine-mediated itch by butorphanol, which activated brain regions with high concentrations of kappa opioid receptors (Figure 4). In addition, fMRI has been able to provide insight into the reward pathways associated with scratching (Yosipovitch et al., 2008). Similarities described between the itch–scratch cycle and both nicotine dependence and obsessive–compulsive

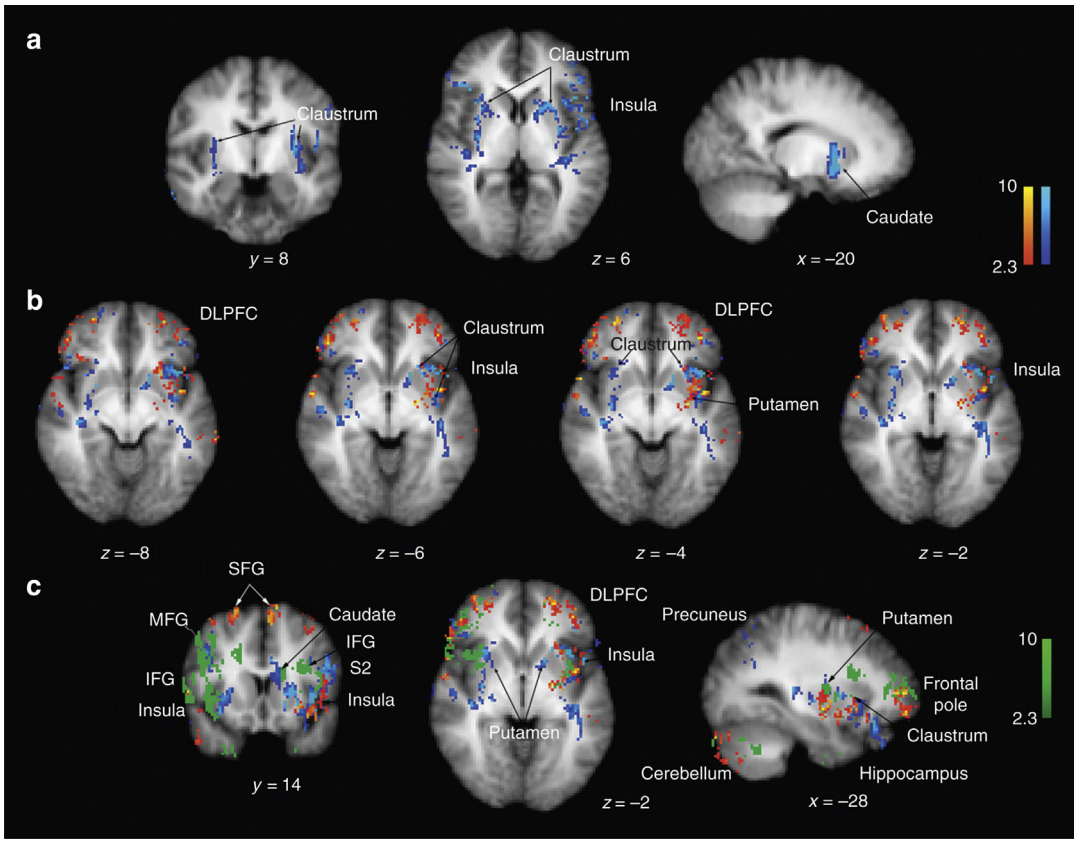

Figure 4. The effect of intranasal butorphanol (1 mg) on cerebral activity analyzed in comparison with that of a placebo (0.9% intranasal saline). (**a**) Butorphanol extensively deactivated bilaterally an area situated between the insular cortex and putamen, which coincides with the anatomic location of the claustrum, while also deactivating the left insular cortex and the putamen. (**b**) The activations induced by histamine itch (red) are overlaid with the deactivations induced by butorphanol (blue vs. placebo), displaying a significant conjunction in the contralateral insula, claustrum, and putamen. (**c**) Overlay of the brain responses induced by histamine itch (red) and cowhage itch (green) and the deactivations induced by butorphanol (blue). x, y, z—MNI standard space coordinates. Z-score > 2.3; $P < 0.05$ (Reprinted from Papoiu et al., 2015 with permission from Elsevier). DLPFC, dorsolateral prefrontal cortex; IFG, inferior frontal gyrus; MFG, middle frontal gyrus; MNI, Montreal Neurological Institute; S2, secondary somatosensory area; SFG, superior frontal gyrus.

disorder (Mochizuki et al., 2015) potentially suggest parallel therapies.

In addition, fMRI studies have also been able to provide insight into the psychological aspects of pruritus. In contagious itch, previous work has shown that patients can experience pruritus when watching videos of other people scratching or of crawling insects (Papoiu et al., 2011). A recent fMRI study also showed a significant increase in itch and scratching in patients with atopic dermatitis while watching an itch-inducing video in comparison with that in those watching a control video (Schut et al., 2017). Of note, the itch induced by watching these videos activated brain regions involved in the frontostriatal circuit, which was not increased in a similar study with healthy patients (Holle et al., 2012). The authors have suggested that this region could be a reasonable target for the treatment of patients with atopic dermatitis (Schut et al., 2017).

Stress is known to be an aggravating factor of pruritus, but the underlying mechanisms have been difficult to elucidate (Liezmann et al., 2011; Suárez et al., 2012). With the goal of localizing areas of the brain associated with stress-induced pruritus, an original fMRI study found that pictures depicting fearful and stressful stimuli invoked pruritus when compared with neutral images. In addition, this study also analyzed fMRI data before treatment and after treatment with sedating antihistamines and nonsedating antihistamines. Each treatment reflected a unique pattern of differences in brain activity, with the sedating antihistamines showing a pattern more congruent with scratching, potentially revealing a more efficacious therapy (Kim et al., 2016).

With advancements in statistical analysis and image processing, the most recent fMRI studies in dermatology are focusing on exploring the functional connectivity of brain regions associated with itch. Initial studies from Mochizuki et al. (2020, 2019) are the first to identify key networks in processing itch. In their most recent study on functional networks of pruritus, Mochizuki et al. (2020) highlight connections with the amygdala and the serotonergic and memory systems possibly representing therapeutic targets.

Finally, with an ever-growing number of functional imaging studies and therefore data, Najafi et al. (2020b) pooled together the first meta-analysis reviewing central mechanisms of itch. With a follow-up study on data from their meta-analysis, these authors hypothesized three major itch matrices, the first two focusing on location and perception and affective and motivational aspects of itch and a third more loosely defined cognitive matrix (Najafi et al., 2021b).

In summary, functional imaging and, more specifically, fMRI continue to evolve and clarify central pathways, ultimately giving us the maps and matrices as tools to better understand the different aspects of itch and ultimately pruritic disease.

Developing insight beyond itch. fMRI has helped to further develop our understanding of the neuropsychological complexities associated with other dermatological diseases such as psoriasis, skin picking disorders, and delusional infestations (Kleyn et al., 2009). Psoriasis has proven similar to both cancer and heart disease with respect to the negative impact on physical and psychosocial well-being (Rapp et al., 1999). Previous fMRI studies have shown that the expression of disgust activates the insular cortex (Phillips et al., 1997). However, Kleyn et al. (2009) reported that patients with psoriasis have significantly smaller signals to disgusted facial expressions than healthy controls. Their fMRI data, along with data from other methods, have helped to show that patients with psoriasis may have developed coping mechanisms for blocking negative social responses, resulting in decreased insula activation (Kleyn et al., 2009). An fMRI study focusing on functional connectivity of pruritic networks in patients with psoriasis showed functional changes in patients with psoriasis compared with those in healthy controls (Najafi et al., 2020a). Understanding that dermatological diseases are able to functionally alter the brain should enlighten care providers to the gravity of deforming skin diseases.

Utilizing fMRI, investigators have begun to undercover the neurophysiology underlying the difficulty to treat abnormal skin sensory conditions. One study of six patients with delusions of infestations showed altered central processing of infestation-related visual stimuli in an fMRI event-related experiment (Eccles et al., 2015). Of particular interest was the increased activity in the amygdala known to be associated with threatening stimuli (LeDoux, 2000). In addition, a case report of a patient with primary delusion infestation undergoing an fMRI experiment showed normalization of brain activity after successful treatment with aripiprazole (Ponson et al., 2015). Another fMRI study of over a dozen patients with excoriation disorders showed that the patients exhibited abnormalities in neurologic regions associated with both habit formation and inhabitation when matched with healthy controls (Odlaug et al., 2016). The studies discussed are all examples of how bettering the understanding of central neurologic patterns with fMRI can lead researchers toward effective therapies.

Next steps for fMRI in dermatological disease. Whereas pruritus has been the focus of many fMRI experiments and much has been learned, each experiment seems to add yet another layer of complexity to an already intricate network. Notably more data on the relationships between the behavioral aspects of pruritus, including stress, anxiety, and depression, should be at the forefront of the focus of studies because there is potential to repurpose known therapies for some of these conditions. Because initial studies of psoriasis have opened the door to a deeper understanding of the longstanding effects of skin deforming conditions on the human brain, an important consideration for study in a formative and vulnerable population is acne vulgaris. Understanding the immediate and long-term effects of variations in the treatment of these patients could lend important insight for potentially more aggressive treatment.

Conclusion

This article has described the basic concepts underlying fMRI studies in order to provide investigators a framework to develop and answer questions regarding the skin–brain axis utilizing this powerful tool. Refining the understanding of functional maps involved in dermatological conditions will continue to provide insight and opportunities to formulate novel therapeutic approaches to chronic dermatological conditions.

Data availability statement

No datasets were generated or analyzed during this study.

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Conceptualization: TSP; Supervision: TSP; Writing – Original Draft Preparation: APF; Writing – Review and Editing: APF, JRB, ABF, JN, TSP

CONFLICT OF INTEREST

The authors state no conflict of interest.

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