COMMENTARY (see article on p. 1074)





# The Brain Network of Itch Distraction

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Itch is a daily experience that is mostly induced by a more or less obvious occurrence on the skin. However, the sensation of itch is something that originates from a pattern of activity changes in various regions of the brain. Therefore, the same skin irritation can induce very different itch perceptions depending on the state of consciousness, on concurrent sensations like pain, touch or scratch, or on distraction. Any of these will change the activation pattern within the affected brain network and the itch perception will be modified. The study of Stumpf et al. (1) focuses on brain areas that may play a role in the distraction from itch. Since it is obvious that the related mechanisms have some common features with the central pain processing, the authors also included regions of the brainstem in their analysis which have been previously described to be involved in pain modulation.

A number of brain imaging studies on the distraction from pain have been performed. Several groups could show that distraction is a process which seems to originate from activation changes in frontal cortical regions, in particular the dorsolateral prefrontal cortex (DLPFC) (2, 3). On the other hand focusing to a stimulus can increase the perceived intensity leading to increased activation of affected brain areas (4). It is assumed that the DLPFC plays an important role in the top-down control of pain and together with the anterior cingulate cortex (ACC) it modulates brainstem regions like the periaqueductal gray (PAG), the rostral ventromedial medulla (RVM), and the locus coeruleus (LC).

Among the brain regions involved in attention modulated perception of pain the PAG has a pivotal role since it drives the descending pain modulation system (5). Do brainstem structures also modulate pruritic input? It seems likely as similar pathways starting at the spinal dorsal horn transmit itch input and pain and these starting points are the targets of the descending system. There are some observations in animal (6) and human studies (7) which indicate that even scratching an itch involves the descending modulation of the PAG.

From this it is a quite interesting approach to study the role of the PAG and other brainstem areas during itch using brain imaging techniques as done by Stumpf et al. (1). For the induction of itch they used a protocol that has been introduced by our group and allows the generation of the typical block design required for fMRI BOLD analysis. With this the sensation of interest (itch) can be easily switched on and off. Further, a modified colour Stroop task was used to distract from the itch. Stroop tasks of different variations have repeatedly been used to distract from pain and its impact on pain related brain areas have been demonstrated (3). The results of the study of Stumpf et al. (1) are surprising: The Stroop task does not reduce itch sensations as shown by the ratings of the subject. Of course, the ratings were given as a summary after a stimulus which could make it difficult for the subject to remember the real experienced sensation when he/she was performing the Stroop task or the Stroop task could be too simple to effectively distract. Interestingly, they describe effects of the distraction on brainstem structures and related cortical regions, although the psychophysical results do not support the effect of the Stroop task. There was an increased activation in the DLPFC, in the PAG and the nucleus cuneiformis (NCF), structures which have been described to be involved in the (pain) modulation system. Could it be that the Stroop task alone can activate the attentional frontal system including the descending system? An indication for this is that an elevated activation occurred within these areas during the Stroop task during itch and during no itch (saline stimulation).

An explanation of these results could be that the "salience network" including the DLPFC is a key structure. This network is involved in the detection of stimuli that could be relevant or that need attention. There is no doubt that a Stroop task requires attention but will this attention be strong enough to suppress itch by activating the descending inhibitory system? Kucyi & Davis (8, 9) report that during distraction from pain by "mind wandering" away from pain the "default mode network" (DMN) is additionally more active and the antinociceptive system increases the functional connectivity between the prefrontal cortex and the PAG. Can these findings from the pain connectome be transferred to the central mechanisms of itch and its centrally mediated suppression? Preliminary results from our group (10) and reports from atopic dermatitis patients (11) suggest that there is an itch related brain network including insular cortex, cingulate cortex, basal ganglia and frontal areas as central nodes and which is increased during itch. The areas mentioned overlap with those which have been described to form the emotional – aversive network of pain processing (12). Due to these commonalities it is very likely that the central modulations of pain and itch are likewise organized.

Stumpf et al. (1) found brainstem activation during the Stroop task in the PAG and the NCF. Indeed, brainstem structures play an important role in the modulation of sensory input and in emotion but considering size and

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complexity of brainstem circuits elucidating their function by imaging is challenging. BOLD signals are harder to detect and anatomical variations have to be considered and usually require either an elaborate normalization procedure (12) or individual analyses. This may be the reason why only a few reports exists about the function of brainstem structures in itch processing. The work of Stumpf et al. (1) shed some light on the role of at least two brainstem structures on this topic, however, many questions about brainstem and itch remain open and therefore the central processing and modulation of the itchy sensations should be pursued and more attention should be given to the role of the brainstem.

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