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Review

The neuronal correlates of intranasal trigeminal function—an ALE meta-analysis of human functional brain imaging data

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ABSTRACT

Almost every odor we encounter in daily life has the capacity to produce a trigeminal sensation. Surprisingly, few functional imaging studies exploring human neuronal correlates of intranasal trigeminal function exist, and results are to some degree inconsistent. We utilized activation likelihood estimation (ALE), a quantitative voxel-based meta-analysis tool, to analyze functional imaging data (fMRI/PET) following intranasal trigeminal stimulation with carbon dioxide (CO_2), a stimulus known to exclusively activate the trigeminal system. Meta-analysis tools are able to identify activations common across studies, thereby enabling activation mapping with higher certainty. Activation foci of nine studies utilizing trigeminal stimulation were included in the meta-analysis. We found significant ALE scores, thus indicating consistent activation across studies, in the brainstem, ventrolateral posterior thalamic nucleus, anterior cingulate cortex, insula, precentral gyrus, as well as in primary and secondary somatosensory cortices —a network known for the processing of intranasal nociceptive stimuli. Significant ALE values were also observed in the piriform cortex, insula, and the orbitofrontal cortex, areas known to process chemosensory stimuli, and in association cortices. Additionally, the trigeminal ALE statistics were directly compared with ALE statistics originating from olfactory stimulation, demonstrating considerable overlap in activation. In conclusion, the results of this meta-analysis map the human neuronal correlates of intranasal trigeminal stimulation with high statistical certainty and demonstrate that the cortical areas recruited during the processing of intranasal CO_2 stimuli include those outside traditional trigeminal areas. Moreover, through illustrations of the considerable overlap between brain areas that process trigeminal and olfactory information; these results demonstrate the interconnectivity of flavor processing.

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Contents

1. Introduction

Everyday chemosensory processing is based partly on the interaction between two systems, the olfactory and the trigeminal system. Whereas the olfactory system mediates the quality percept of an odor, the trigeminal system conveys sensations such as a burning, pungency, or stinging, as well as touch, pressure, and temperature. Although the processing of olfactory stimuli has received much attention, the neurological substrate of intranasal trigeminal function remains poorly understood. Further investigations of the intranasal trigeminal system are of great importance to an understanding of its role as a sentinel against potentially toxic substances and as the mediator of more animated percepts of odors and flavors.

Our current understanding of mechanisms underlying trigeminal stimulus processing is derived mostly from animal models (for review see Langley et al., 2008; Mogil, 2009). In both animals and humans, the nasal mucosa is innervated by the ophthalmic and maxillary branches of the trigeminal nerve, which transfers information about a painful stimulus to trigeminal nuclei in the spinal cord (Anton et al., 1991). From there, information is relayed via the lateral and the medial pain systems, two parallel organized systems with distinct projections (de Leeuw et al., 2005). The lateral pain system transmits information to lateral thalamic structures, which project to the primary (S I) and secondary (S II) somatosensory cortices. The medial pain system transfers information to medial thalamic nuclei and from there to prefrontal cortex, insula, cingulate gyrus, brain stem, and to the limbic system (Ingvar and Hsieh, 1999; Treede et al., 1999; Wiech et al., 2001). Significant genetic, neurochemical, and neuroanatomical differences distinguish non-human and human processing and experience of pain-related stimuli, as demonstrated by recent findings (Craig, 2009). Among other implications, these conclusions suggest that although animal models may provide an approximation of basic human trigeminal processing, there is no substitute for human subjects in the quest to reach a full understanding of how the human brain processes trigeminal stimuli.

Investigations of the human trigeminal system frequently rely on psychophysical or electrophysiological methods (Hari et al., 1997; Hummel and Kobal, 1999; Hummel and Livermore, 2002; Huttunen et al., 1986; Kobal and Hummel, 1988; Rombaux et al., 2006), which yield results that allow only indirect inferences of underlying cerebral processes due to methodological limitations. Psychophysical and electrophysiological tools lack direct links to functional processing and provide low spatial specificity. In contrast, non-invasive methods of functional brain imaging allow us to understand trigeminal processing with higher spatial resolution. In conjunction with these methods, the use of pure trigeminal stimuli, typically carbon dioxide (CO_2), an odorless gas that stimulates the trigeminal system almost exclusively, enables isolation of an intranasal trigeminal sensation from an accompanying odor sensation (Fröhlich, 1851; Shusterman and Balmes, 1997; Stevens et al., 1982; Thürauf et al., 1991). Similarly, studies investigating olfactory processing often opt to use pure odorants that do not stimulate the trigeminal system, such as phenyl ethyl alcohol (PEA) or hydrogen sulfide (H_2S) (Doty et al., 1978; Kobal et al., 1989).

Several comparisons of brain activation originating from stimulation with pure trigeminal stimuli to activation originating from stimulation with pure odorants have demonstrated considerable overlap in the structures mediating functional processing in each system (Boyle et al., 2007; Hummel et al., 2005,2009a,b; Iannilli et al., 2008; Schoepf et al., 2009). Whereas pure trigeminal stimuli typically activate the brain stem, thalamus, caudate nucleus, anterior and dorsolateral orbitofrontal cortex, medial frontal gyrus, frontal operculum, superior temporal gyrus, cingulate, and the postcentral gyrus, stimulation with pure odors commonly induces activation in the medial orbitofrontal cortex, amygdala, parahippocampal gyrus, and cerebellum, exclusively. Functional overlaps between the trigeminal and olfactory networks were observed in the