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Using Structural and Functional Brain Imaging to Investigate Responses to Acute Thermal Pain

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Abstract: **Despite a fundamental interest in the relationship between structure and function, the relationships between measures of white matter microstructural coherence and functional brain responses to pain are poorly understood. We investigated whether fractional anisotropy (FA) in 2 white matter regions in pathways associated with pain is related to the functional magnetic resonance imaging (fMRI) blood oxygen level-dependent (BOLD) response to thermal stimulation. BOLD fMRI was measured from 16 healthy male subjects during painful thermal stimulation of the right arm. Diffusion-weighted images were acquired for each subject and FA estimates were extracted from the posterior internal capsule and the cingulum (cingulate gyrus). These values were then included as covariates in the fMRI data analysis. We found BOLD response in the midcingulate cortex (MCC) to be positively related to FA in the posterior internal capsule and negatively related to FA in the cingulum. Our results suggest that the MCC's involvement in processing pain can be further delineated by considering how the magnitude of the BOLD response is related to white matter microstructural coherence and to subjective perception of pain. Considering relationships to white matter microstructural coherence in tracts involved in transmitting information to different parts of the pain network can help interpretation of MCC BOLD activation.**

Perspective: ***Relationships between functional brain responses, white matter microstructural coherence, and subjective ratings are crucial for understanding the role of the MCC in pain. These findings provide a basis for investigating the effect of the reduced white matter microstructural coherence observed in some pain disorders on the functional responses to pain.***

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Key words: *Acute pain, functional magnetic resonance imaging, diffusion tensor imaging, fractional anisotropy, multimodal imaging.*

Pain is a complex, multidimensional, conscious experience. As such, the processing of painful stimuli is subserved by a number of cortical and subcortical regions. The functional cortical response to pain is commonly measured using blood oxygen level-dependent (BOLD) functional magnetic resonance imaging (fMRI) and it is generally agreed that a number of cortical brain regions are involved in processing acute pain. This network of regions not only involves the somatosensory cortices but also a number of other brain regions such as the anterior cingulate cortex (ACC), midcingulate cortex (MCC), insula, and prefrontal cortex. These regions are not pain-specific but are involved in the detection of salient stimuli, stimulus evaluation, and coordinating behavioral responses to stimuli.[1,33] The interaction between these regions at various stages of pain processing is relevant to the basic understanding of pain and to the treatment of pain conditions.

The transmission of neural information during pain processing requires a complex network of white matter

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(WM) structures. The microstructural coherence of WM in these structures contributes to the efficiency of signal propagation through these tracts. Diffusion tensor imaging (DTI) has become a popular method for investigating brain microstructure in health and disease.[20] The diffusion tensor directionality is usually quantified by fractional anisotropy (FA), which is commonly considered as an overall neuroimaging index of WM integrity (or microstructural coherence),[4,24] as such, FA is a robust and well established DTI metric reflecting WM microstructural coherence. Decreased myelination and/or axonal density can lead to reduced FA, as such, lower FA values are associated with reduced WM microstructural coherence. Such measures of brain structure are related individual differences in many behavioral measures (eg, motor skills, cognition, perception, and personality).[22] However, the predictive power of this anatomical information for the evaluation of individual differences is not fully established.[22]

Measures of brain structure and function, their relation to each other, and to behavioral variables can be used to exploit these individual differences to provide insight into the mechanism underlying pain processing.[48] For example, factors such as pain perception, pain sensitivity, and pain threshold vary across individuals. In addition, some of these individual factors have also been related to brain imaging measures, for example, pain sensitivity is related to BOLD response[7] and cortical thickness,[11] FA has been related to pain intensity.[29] In addition, functional and anatomic changes in response to repetitive pain stimulation have also been observed,[5,47] suggesting a degree of plasticity in these measures.

Despite such a fundamental interest in the relationship between structure and function, the relationships between measures of WM microstructural coherence and functional brain responses to pain are poorly understood. In particular, it is not clear whether there is likely to be a positive or negative relationship between these measures and what such relationships might mean in terms of the functional response to pain. For example, a systematic review by Warbrick et al, (unpublished) showed that FA is generally positively related to the magnitude of the BOLD response in sensory regions but for higher order functions positive and negative relationships were observed depending on the nature of the task. Because pain involves sensory and higher order (cognitive and affective) processes, the relationship between BOLD response and FA in brain regions involved in pain processing could be positive, negative, or not exist at all. The nature of these relationships in regions having multiple roles could tell us more about the functions they perform. For example, better WM microstructural coherence should facilitate processing in the regions it connects and its relationship to decreased or increased BOLD response in a particular region can indicate its current function/performance (eg, processing efficiency or improved sensory input). The ability to identify these relationships for specific regions can provide insight into the different roles they perform and the underlying neural mechanisms.

We investigated whether FA in 2 WM regions known to be involved in pain-related pathways is related to the BOLD response in cortical regions in response to thermal stimulation. The premise of our approach is that information transfer via WM tracts depends on the condition of the whole tract and that the integrity of the whole tract will influence the functional responses observed. We focused on the posterior internal capsule (IC), which contains sensory fibers including ascending pain fibers[17] and the cingulum, which has connections to regions involved in pain processing.[21,49] We also investigated whether these imaging measures are related to the subjective ratings of the thermal stimuli.

Methods

The study protocol was approved by the local Human Subjects Review Board at RWTH Aachen University and was carried out in accordance with the Declaration of Helsinki. Subjects were recruited via flyers, word of mouth, and newsletter alerts. Written informed consent was obtained from all subjects.

Subjects

Twenty healthy, right-handed male subjects participated in this study. Handedness was assessed using the Edinburgh handedness scale.[35] Subjects were assessed by experienced interviewers using a short version of the semistructured clinical interview[39] to screen for psychiatric disorders; responding with 'yes' to any of the entry questions for each disorder would result in exclusion from the study. The Beck Depression Inventory[3] was administered to exclude subjects with depression. No subjects were excluded because of depression or responses during the semistructured clinical interview. German versions of all questionnaires were used. Four subjects were excluded from analyses (1 because of excessive movement during scanning [more than the size of 1 voxel: 3 mm], 1 because of high state anxiety scores, and 2 because button responses were not being logged correctly). The mean age of the 16 subjects included in the analyses was 28.31 years (SD = 4.21).

Procedure and Stimulation

After completing the informed consent procedure subjects completed the State-Trait Anxiety Inventory.[44] All thermal stimulation was carried out with a PATHWAY Model ATS (Advanced Thermal Stimulator) and a standard (30 mm $\times$ 30 mm) magnetic resonance compatible thermode (Medoc Ltd, Ramat Yishai, Israel). Stimuli were delivered to the right forearm of the subject and the thermode was moved after every stimulus to prevent habituation effects. The area for moving the thermode was approximately 3 times the size of the thermode and the area stimulated for consecutive stimuli did not overlap. As a result the minimum duration before restimulation of an area was 46 seconds (1 stimulation plus 2 baseline periods). The first part of the experimental procedure involved calibrating the stimulation level for each subject. Fifteen stimuli were delivered; each stimulus

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