Somatotopic Representation of Nociceptive Information in the Putamen: An Event-related fMRI Study

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The ability to locate pain plays a pivotal role in immediate defence and withdrawal behaviour. However, it is unclear to what extent nociceptive information is relayed to and processed in subcortical structures relevant for motor preparation and possibly the generation of withdrawal behaviour. We used single-trial functional magnetic resonance imaging (fMRI) to assess whether nociceptive information is represented in the putamen in a somatotopic manner. We therefore applied thulium–YAG laser-evoked pain stimuli, which had no concomitant tactile component, to the dorsum of the left hand and foot to 15 healthy subjects in a randomized order. In addition, 11 subjects were stimulated on the right body side. Differential representations of hand- and foot-related blood oxygen level dependent (BOLD) responses within the putamen were assessed using a single subject approach. Nociceptive stimuli significantly activated the putamen bilaterally. However, a somatotopic organization for hand- and foot-related responses was only present in the contralateral putamen. Here the foot was located anteriorly and medially to the hand, which parallels results from anatomical and microstimulation studies in monkeys and also human imaging data on the arrangement of movement related activity in the putamen. This result provides evidence for the hypothesis that behaviourally relevant nociceptive information without additional information from the tactile system is represented in the putamen and made available for pain related motor responses.

Keywords: laser, nociception, putamen, single trial fMRI, somatotopy

Introduction

The consequence of an acute noxious stimulus encountered by a conscious organism is most often a motor response to withdraw or escape. The absence of movement following a painful event may result in severe tissue damage or death. At the lowest level this is implemented through spinal cord reflexes (Skljarevski and Ramadan, 2002), but more complex avoidance behaviour requires a more sophisticated response likely to be generated in the brain. Thus, the ability to locate the origin of a noxious stimulus is essential for the adoption of such spatially oriented withdrawal actions.

Although there has been extensive research on the central mechanisms involved in the sensory-discriminative dimensions of pain (Porro *et al.*, 1998; Apkarian *et al.*, 1999; Coghill *et al.*, 1999; Bornhovd *et al.*, 2002; Ploner *et al.*, 2002), little is known about the central mechanisms responsible for integrating incoming nociceptive information that results in a coordinated motor response.

Electrophysiological data revealed that the basal ganglia receive nociceptive and non-noxious somatosensory information (Schneider and Lidsky, 1981; Bernard *et al.*, 1992; Chudler *et al.*, 1993a): However, the functional significance of nociceptive sensory-motor integration in the basal ganglia is not well understood. A crucial aspect regarding defensive behaviour is whether spatial information of a provoking noxious stimulus is processed within structures relevant for the generation of withdrawal behaviour, such as the basal ganglia.

Previous work demonstrated that a very basic form of spatial coding, i.e. laterality of pain stimuli, is not only preserved in target regions of the afferent neuraxis, such as thalamus, SI, SII and posterior insula (Coghill *et al.*, 2001; Brooks *et al.*, 2002; Bingel *et al.*, 2003), but also in structures of the motor output system, which are relevant for the generation of spatially guided defensive behaviour, such as putamen, red nucleus and cerebellum (Bingel *et al.*, 2002).

On the grounds that the putamen is capable to encode both stimulus-laterality (Bingel *et al.*, 2002) and stimulus intensity (Chudler and Dong, 1995), it is plausible that this area could also encode a more fine-grained aspect of somatotopy, namely the differential representation of different body parts in order to make spatial information about the noxious (provoking) stimulus available for a defensive response.

The purpose of this study was to investigate whether the representation of selective noxious stimuli in the putamen is somatotopically organized. Therefore, we used a thulium (Tm)–YAG (yttrium–aluminium–granate) laser to apply sudden, unexpected and selective noxious stimuli in a randomized order to hand or foot of the left and right body side. To test the hypothesis of somatotopic organization of nociceptive information in the putamen, we studied blood oxygen level dependent (BOLD) responses in the ipsi- and contralateral putamen using an event-related fMRI design in a single subject approach.

Materials and Methods

Subjects

Twenty healthy subjects (two female) all right-handed, aged 20–34 years (mean 28) gave written informed consent to participate in the study, which was conducted in accord with the declaration of Helsinki and approved by the local ethics committee. All subjects had normal pain thresholds on both sites of stimulus application, no history of neurological or psychiatric disease and were free to withdraw from the study at any time.

Laser Stimulation

A Tm–YAG infrared laser (Neurolaser; BAASEL Lasertech, Starnberg Germany) was used to apply computer-controlled brief radiant pain stimuli. The Tm–YAG laser emits near-infrared radiation (wavelength 1.96 μm, spot diameter 5 mm, pulse duration 1 ms) with a penetration depth of 360 μm into the human skin. The laser stimulus allows precise restriction of the deposited heat energy to the termination area of primary nociceptive afferents (20–570 μm), without damaging the epidermis or affecting the subcutaneous tissue (Spiegel *et al.*, 2000). All ferromagnetic components belonging to the laser head used inside the scanner room were replaced by brass parts. The main laser

device was located in the MR control room and connected to the laser head in the magnet room with an optical fiber of 10 m length, transmitting the laser light. Individual pain thresholds for the site of stimulus application were determined outside the scanner on a separate occasion, but within 1 week before the MR experiment.

Experimental Protocol

In 15 subjects, 50 selective noxious cutaneous laser stimuli were randomly applied to the dorsum of the left hand or foot (25 stimuli each) in a single fMRI session. In six of these and in five additional subjects (total of 11), the same procedure was performed on the right body side as well. For those subjects, who received two consecutive sessions, the side of stimulus application was balanced over the sessions. Stimulus application was computer-controlled (Software Presentation; www.neurobehavioralsystems.com) and unpredictable, invisible and inaudible to the subject. To avoid sensitization and habituation, the stimulus site was systematically varied after each stimulus. For the hand-stimulation, an energy level of 600 mJ was used. This choice was based on previous fMRI and psychophysical experiments, indicating that 600 mJ stimuli applied to the dorsum of the hand evoke a brief but clearly 'pin-prick-like' painful sensation without any warmth or tactile components (Bromm *et al.*, 1984; Spiegel *et al.*, 2000; Buchel *et al.*, 2002). This intensity reliably activates both cortical and subcortical structures. (Bingel *et al.*, 2002; Bornhovd *et al.*, 2002; Buchel *et al.*, 2002). To account for an increased pain-threshold of the foot (Devos *et al.*, 2000), a 650 mJ stimulus was used for foot stimulation. The stimulus site (hand versus foot) and the inter-stimulus-interval (between 8 and 12 s) were fully randomized. Rating of the perceived pain intensity was not requested in order to minimize additional motor or working memory components. After scanning, all subjects reported that the stimuli were moderately and comparably painful for both sites of stimulus application.

Image Acquisition

MR scanning was performed on a 1.5 T MRI system (Siemens Vision). A high resolution ($1 \times 1 \times 1$ mm voxel size) T_1-weighted structural MRI was acquired for each volunteer using a 3-D FLASH sequence. A total of 382 fMRI scans (20 axial, 3 mm thick slices each, 1 mm gap) were acquired using a gradient echo echo-planar (EPI) T_2^* sensitive sequence (T_R 1.6 s, T_E 40ms, flip angle 90°, matrix 64×64, field of view 210×210mm). The images were oriented slightly tilted towards the AC–PC line and aligned so that the sample included primary as well as secondary somatosensory cortex. Subjects' heads were positioned in a standard head coil with foam pads.

Image Processing and Statistical Analysis

Image processing and statistical analysis were carried out using SPM99 (Friston *et al.*, 1995b; Worsley and Friston, 1995; http://www.fil.ion.ucl.ac.uk/spm). All volumes were realigned to the first volume (Friston *et al.*, 1995c), spatially normalized (Friston *et al.*, 1995a) to a standard EPI template (Evans *et al.*, 1993) and finally smoothed using a 6 mm isotropic Gaussian kernel. The T_1-weighted structural data was co-registered to the functional scans by normalizing it to a T_1-weighted template in the same space as the T_2^* EPI template used to normalize the functional data set. Data analysis was performed by modelling the different trials (pain foot, pain hand) as delta functions convolved with a canonical haemodynamic response function as implemented in SPM99. Inspection of the plotted responses revealed that responses evoked by laser stimuli at the foot were delayed by 0.5–1 s on average. We therefore also delayed the HRF model for foot responses by 0.5 scan (0.8 s). Voxel-wise regression coefficients for both regressors were estimated using least squares within SPM99 (Friston *et al.*, 1995c). To reduce the risk that putamen activation could be movement-correlated, movement parameters derived from the realignment procedure were included as covariates of no interest. Effects were tested with appropriate linear contrasts of the regression coefficients (parameter estimates), resulting in a *t*-statistic for each voxel. These *t*-statistics constitute a statistical parametric map (SPM), interpreted by reference to the probabilistic behaviour of Gaussian random fields (Worsley, 1994). SPMs were computed for each of the stimulus conditions (hand and foot) for each individual. To allow for the identification of activation peaks in each individual, a rather liberal threshold of $P < 0.01$ uncorrected was chosen for the activation in the single subject.

Assessment of Somatotopic Organization

For the majority of subjects, foot stimulation resulted in significantly stronger activation compared to hand stimulation throughout the whole volume sampled. Consequently somatotopic organization could not be assessed simply by statistically contrasting hand with foot stimulation. Therefore, to test for the hypothesis of somatotopic organization in the putamen, the MNI-coordinates of the most significant voxel (activation peak) within the putamen were identified for each stimulus condition (Jueptner *et al.*, 1997; Ruben *et al.*, 2001). This was done for the group and for each individual. For the identification of the activation of peak activation within the putamen a template/ROI of the putamen was created based on the canonical T_1 implemented in SPM99. This standard ROI was then applied as search volume for the peak activation in each single subject. With this approach we aimed to avoid the bias by manually selecting peak activations, which might be mixed especially with insular activation, when selection should be made individually for each subject. To statistically test for the differences between peak activation sites between hand and foot we used a multivariate linear model (Hotelling's T_2^2 test) for dependent samples. To further investigate differences in individual directions the coordinates of each orthogonal direction (x, y, z) were compared separately with a univariate *t*-test. A difference was accepted to be significant at $P < 0.05$.

Psycho-physiological Interaction

To investigate the context dependent contributions of putamen activity during noxious stimulation a psycho-physiological interaction (PPI) (Friston *et al.*, 1997) analysis was performed. A PPI means that the contribution of one area to another changes significantly with the experimental or psychological context. The contribution can be seen as modulating the responses evoked by a stimulus (in our case, pain). In other words the PPI analysis reveals which areas show activation patterns covarying with putamen activity depending on whether the foot or hand is stimulated.

Time series for the contralateral putamen were extracted for each individual volunteer using the first eigen-timeseries (principal component) from all voxels in the putamen ROI as described above.

The PPI regressor was computed as the element-by-element product of the mean-corrected putamen activity and a vector coding for the differential effect of hand and foot noxious stimulation (1 for hand noxious stimulation, –1 for foot noxious stimulation). Our analysis of functional connectivity was thus specific for context-dependent putamen influences that occurred over and above any task effects and context-independent putamen influences. Brain sites receiving contextual putamen influences that were stronger during hand than during foot noxious stimulation were determined by a *t*-test. To test for effects across the group of subjects a random effects analysis was performed.

Results

Painful laser stimulation to the hand and foot led to statistically significant increases in fMRI signal intensity in several cortical areas. In this report we focus on pain-related responses in the putamen. Responses outside the putamen are beyond the scope of this paper and will be reported elsewhere. In short, the primary somatosensory cortex (SI) showed clear somatotopic organization ipsi- and contralaterally to painful stimulation. Furthermore, a differential representation of hand and foot stimulation appeared within the contralateral opercular-insular cortex.

Putamen Single Subject Analysis

Laser stimulation failed to evoke significant putamen activation according to our requested threshold in either of the stimulus conditions in the contralateral putamen in four subjects (HN, SB, FK and MS) and in ipsilateral putamen in six subjects (AM,

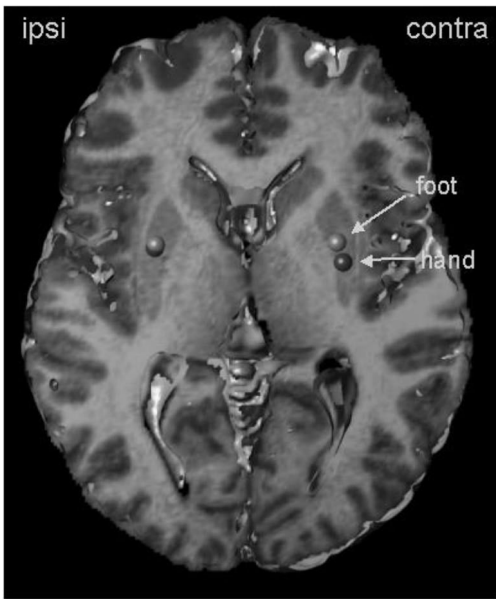

Figure 1. Differential representation sites of the hand- and foot-related laser-evoked pain in the contralateral putamen. Hand and foot representation of laser-evoked fMRI responses in ipsilateral and contralateral putamen overlaid on a normalized T_1-weighted image. Mean distributions of peak activation are illustrated by a sphere centred around the mean coordinate. Foot-related distribution is depicted in green, hand-related responses in red. Data from left- and right-sided stimulation were pooled for this illustration. To spatially overlay results for both sides of stimulus application, the results of the right-sided stimulation were mirrored along the *z*-plane (R–L flipped). Accordingly, responses contralateral to noxious stimulation (independent of the side of stimulation) are shown on the right, while responses in the putamen ipsilateral to nociceptive stimulation are shown on the left side. See online Supplementary Material for a colour version of this figure.

DG, UB, HN, MS, OT). These subjects were not included in the statistical comparison of the coordinates of peak activation of hand and foot stimulation. Subsequently, our assessment of a somatotopic representation in the contralateral putamen was based on 22 subjects/session, 13 of which with left and nine with right-sided noxious stimulation. For the evaluation of the ipsilateral putamen, the data of 20 subjects/session was pooled (12 left-, 8 right-sided stimulation).

The single subject data of contralateral noxious stimulation is presented in the online Supplementary Material, Tables 1 and 2.

Group Analysis

To allow general inferences about a somatotopic arrangement in the contra- versus ipsilateral putamen, the data of all subjects were pooled. To spatially overlay activations in homologue (i.e. contralateral) brain areas for both sides of stimulus application, the statistical maps of those subjects with right-sided stimulation were mirrored along the *y*-axis (R–L flipped). After this procedure, contralateral activations of both sides of stimulus application were overlaid in the same space. The same was procedure was applied to ipsilateral activations.

Pooling both sides of stimulus application reveals a distinct representation for the hand and foot under noxious stimulation in the contralateral putamen [Hotelling's T_2^2, $F(3,19) = 3.2$, $P < 0.05$, ±30.5, –4.4, 1.9 versus ± 28.6, 2.0, 1.5 in *x*, *y*, *z* for hand versus foot stimulation], with the foot being represented medially ($P < 0.05$) and anteriorly ($P < 0.005$) to the hand (see Fig. 1). In contrast, there was no difference of the peak activations for hand and foot noxious stimulation in the ipsilateral

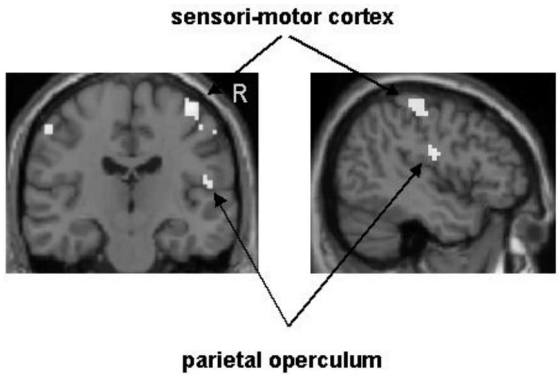

Figure 2. Areas showing a significant covariation with putamen activity during noxious stimulation of the hand. The results from the psycho-physiological interaction analysis overlaid on a normalized T_1-weighted image. Covariation of activity in the sensori-motor cortex and the parietal operculum with activity in the putamen are stronger during noxious stimulation of the hand. To spatially overlay results for both sides of stimulus application, the results of the right-sided stimulation were mirrored along the *z*-plane (R–L flipped). Accordingly, responses contralateral to noxious stimulation (independent of the side of stimulation) are shown on the right, while responses in the putamen ipsilateral to nociceptive stimulation are shown on the left side. See online Supplementary Material for a colour version of this figure.

putamen (Hotelling's T_2^2, $F(3,17) = 0.15$, n.s. ±29.7, 0.3, –0.5 versus ±29.4, 1.3, 0.3 in *x*, *y*, *z* for hand versus foot stimulation).

Psycho-physiological Interaction Analysis

For noxious stimulation of the hand, we found a stronger covariation of putamen activation with the hand representation within the primary sensori-motor cortex [contralateral, 39, –18, 63 ($Z = 4.4$); ipsilateral, –45, –33, 57 ($Z = 4.1$)] as well as the contralateral parietal operculum [33, –30, 51 ($Z = 4.4$)]. The activation in primary sensori-motor cortex was pronounced contralateral to noxious stimulation (therewith ipsilateral to the respective putamen activation).

The results of the opposite test, namely for significantly stronger covariation in response to foot compared to hand noxious stimulation did not reveal any significant results.

In general noxious stimulation of the hand results in more robust cortical activations compared to stimulation of the foot. This parallels experiences from a recent fMRI study comparing tactile stimulation of hand and foot stimulation (Ruben *et al.* personal communication) and previous ERP and MEG studies, also indicating that laser stimulation of the foot evokes significantly smaller signal than hand stimulation (Spiegel *et al.*, 2000; Lorenz *et al.* and Ploner *et al.*, personal communication). Therefore, the negative finding of the psycho-physiological interaction analysis with respect to foot stimulation might be related to an insufficient signal-to-noise ratio.

Discussion

General Aspects and Experimental Design

To investigate, whether the putamen provides a somatotopic representation of nociceptive information, laser pain stimuli were randomly applied to the left and right dorsum of the hand and foot and BOLD activity reflecting neuronal response was assessed with event-related fMRI. The stimulus quality of the laser is ideal for the evaluation of a distinct discriminative aspect of pain, as the central processing of nociceptive spatial

information. Statistical comparison of peak activation in each single subject revealed different peak coordinates for the hand and foot in the contralateral putamen. The differential, namely somatotopically organized representation in the contralateral putamen illustrates that selective nociceptive information about the stimulus location is relayed to and processed in this area in the absence of tactile information. In contrast, no such somatotopy was present in the ipsilateral putamen.

Somatotopic Representation of Nociceptive Information in the Putamen

The importance of the basal ganglia in motor response is well established: they are linked to (i) planning the execution of learned motor behaviour (ii) controlling voluntary movement and, most importantly with respect to the experience of pain, (iii) the coordination of context-dependent movements (DeLong *et al.*, 1984; Alexander *et al.*, 1990; Graybiel, 1990; Hikosaka, 1991; Kropotov and Etlinger, 1999). However, little is known about how the basal ganglia process and integrate nociceptive information relevant to guide such movements (Chudler and Dong, 1995; Nishino *et al.*, 1991).

Electrophysiological studies exploring the non-nociceptive and nociceptive response properties of basal ganglia neurons indicate that (i) many neurons in the putamen are activated exclusively or differentially by noxious stimulation (Schneider and Lidsky, 1981; Chudler *et al.*, 1993a) and (ii) some of these even encode stimulus intensity (Chudler and Dong, 1995; Chudler, 1998), which might be related to grading motor responses. Accordingly, activation in the putamen has been observed in previous neuroimaging studies of pain (Iadarola *et al.*, 1998; Coghill *et al.*, 1999; Derbyshire *et al.*, 1999; Hui *et al.*, 2000).

Knowledge about whether and how putamen neurons spatially encode nociceptive information is relatively sparse and limited to single-cell recordings in the anaesthetized animal (Chudler *et al.*, 1993b). The majority of investigated striatal neurons had large, bilateral receptive fields including the entire body. However, one study did report a somatotopic arrangement of nociceptive neurons within the striatum of the rat (Richards and Taylor, 1982). A recent study by our group revealed an asymmetric response (i.e. stronger for the side contralateral to stimulation) to pain in the putamen indicating that nociceptive spatial information of the stimulated body side is preserved in the contralateral putamen (Bingel *et al.*, 2002). Here, we extend these findings by showing that a more precise form of spatial information – that of the stimulated body part (arm versus leg) – is also preserved in the contralateral putamen. More specifically, in the contralateral putamen the foot representation appears to be represented anteriorly and medially to the hand. This somatotopic arrangement with the foot representation anterior to the hand parallels results from anatomical (Kunzle, 1977) and microstimulation studies in monkeys (Crutcher and DeLong, 1984), but also human imaging data on the somatotopic arrangement of motor responses in the putamen (Maillard *et al.*, 2000). In the monkey, the labelling of projections from the post-central leg and trunk area leads to grain accumulation rostrally (= anteriorly) compared to those from the face and arm area (Kunzle, 1977) and single-cell activity from active movements and somatosensory input shows an organization along the anteroposterior axis of the putamen, with leg representing neurons being less common in the caudal putamen (Crutcher and DeLong, 1984). Two recent human fMRI studies on the somatotopic organization of movement-related activity from different body parts also showed activation related to toe-movement anterior to finger-movement in the putamen (Maillard *et al.*, 2000; Gerardin *et al.*, 2003). In both studies the motor representation of the toe was slightly medial to the finger representation, although this difference was not significant, perhaps because of the limited number of subjects studied. In contrast to other studies (Kunzle, 1977; Alexander and DeLong, 1985; Lehericy *et al.*, 1998; Maillard *et al.*, 2000; Gerardin *et al.*, 2003), we did not find a dorso-ventral gradient of the foot and hand representation. The absence of a somatotopic organization in the ipsilateral putamen parallels the results from motor studies on somatotopy (Lehericy *et al.*, 1998; Maillard *et al.*, 2000; Gerardin *et al.*, 2003) and is in line with the lateralized input into the putamen from both peripheral or cortical sources (Kunzle, 1977; Richards and Taylor, 1982).

The increased coupling of primary sensori-motor cortex (SM1) and the parietal operculum with the putamen during noxious stimulation of the hand may indicate the potential source of noxious input into the putamen. In contrast one may also imagine that noxious information in the putamen modulates higher cortical areas. Interestingly, the revealed functional connectivity of the putamen parallels anatomical information available in the primate on the topography of inputs to the basal banglia from the somatosensory and the motor cortex (Kemp and Powell, 1970; Kunzle, 1975, 1977; Chikama *et al.*, 1997). Neuro-anatomical evidence also suggests that nociceptive information may reach the putamen by subcortical afferent sources (e.g. cortex, thalamus and dorsal raphe nucleus (Chudler and Dong, 1995).

The temporal resolution of fMRI does not allow dissociating primarily sensory or secondary motor related responses. However, our present finding of spatially distinct BOLD responses to nociceptive information arising form different body parts in the contralateral putamen strengthens the view that spatial information of a noxious event is relayed to and preserved in the basal ganglia to make this information available for defence and avoidance behavior. The somatotopically organized responses might reflect the basis for preparation, but also inhibition of motor reactions related to pain, in particular withdrawal behaviour, which is aimed at the limb affected by the provoking stimulus.

In conclusion our study provides evidence that spatial information of selective nociceptive information is relayed to and processed in the contralateral putamen, underlining the importance of the putamen for the integration of somatosensory and motoric information relevant to coordinate context-dependent motor responses.

Supplementary Material

Supplementary material can be found at:
http://www.cercor.oupjournals.org/

Notes

We thank the Physics and Methods group at NeuroImage Nord in Hamburg, the technical staff at the Department of Neurophysiology for their support with the laser and Professor Eric Chudler and Désirée Gonzalo for suggestions on an earlier draft of this paper. This work was supported by the Volkswagenstiftung.

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