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Abnormal somatosensory activation patterns in orofacial dystonia and their modulation by botulinum toxin examined by a fully automated tactile stimulation device in fMRI.

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To Andrea

1.1 Clinical findings and classification of dystonia

Dystonia is a movement disorder characterized by involuntary muscle contractions with spreading muscle activity to adjacent muscle groups causing twisting movements and abnormal postures (Fahn, 1988).

It is classified by etiology, age of onset and body distribution. Primary dystonia develops spontaneously and shows no pathological correlate in anatomical brain scans. Monogenetic forms of primary dystonia with mainly autosomal dominant inheritance were identified with several gene Grammar loci for the different types, e.g. DYT13 for multifocal and segmental dystonia or DYT7 for adult-onset focal dystonia (Klein et al., 2007). Variable penetrance led to a “second hits theory” triggered by environmental (Lee et al., 2004) and individual factors, such as injury, hypoxia and viral infection (Saint Hilaire et al., 1991; Edwards et al., 2003) or emotional and physical stress (Dobyns et al., 1993). Secondary forms can be caused by structural brain lesions, pharmaceuticals (e.g. neuroleptics) and metabolic diseases (Fahn et al., 1998, Friedman and Standaert 2001). Further dystonia manifests in hereditary neurodegenerative diseases and dystonia-plus syndromes (Breakefield et al., 2008). Classification regarding disease outbreak is prognostically important, since early onset forms tend to generalize from single limb affection to severe generalized forms. Late onset dystonia however shows lower tendency to progression and remains focal or segmental, mainly in craniocervical location (Bressman et al., 2004).

Dystonia appears in focal forms affecting a single region only, a segmental form with two or more adjacent regions, a multifocal form with more than two non- adjacent regions and a generalized form. Dystonia in ipsilateral upper and lower extremities is referred to as hemidystonia.

In this study we examined two cranial subtypes of focal dystonia, Blepharospasm and Meige's syndrome.

1.1.1 Blepharospasm and Meige’s Syndrome

Blepharospasm is the most prevalent form of cranial dystonia with clinical manifestation of involuntary and frequent eye blinking and problems with voluntary eye opening (Berardelli et al., 1998; Hallett 2002). Symptoms may be provoked by stimuli like bright light, reading and emotional stress. It shows a prevalence of 17-133 cases per million preferring the

female gender (Defazio et al., 2007) with a mean age of onset of 56 years for blepharospasm and oromandibular dystonia (O'Riordan at al., 2004).

Blepharospasm as a focal form of dystonia may spread to adjacent body areas, especially to neck, jaw, larynx and pharynx, and turn into Meige's syndrome with greatest risk to do so within the initial five years of history (Defazio et al., 1999; Defazio et al., 2007; Abbruzzese et al., 2008). Meige's syndrome is the combination of blepharospasm and orofacial symptoms such as dystonia of the lips, tongue or pharynx.

1.1.2 Botulinum toxin in the therapy of focal dystonia

Botulinum toxin (BTX) is a bacterial neurotoxic protein produced by spore forming clostridium botulinum. Injected in a dystonic muscle, it inhibits presynaptical acetylcholine release from motoneurons into the neuromuscular junction (Montecucco and Schiavo, 1995). BTX is a dimer protein consisting of a 100-kd heavy and 50-kd light chain connected by a single disulfide bond (Lacy et al., 1998). Entering the synaptic endings via endocytosis at the terminal nerve ending, the light chain degenerates binding proteins, particularly SNARE proteins, which are essential for exocytosis of acetylcholine. Two types of botulinum toxin with specific target proteins are commonly used in medicine: type A cleaving the protein SNAP-25, type B targeting synaptobrevin (Arnon et al., 2001). Inactivation of synaptic fusion complexes and reduction of acetylcholine release leads to reduced muscle activity and alleviates dystonic symptoms in affected muscles. Patients with blepharospasm clinically profit up to 94% from BTX injection into the musculus orbicularis oculi with an average latency from three to five days and a lasting benefit from three to four months. To prevent the induction of antibodies, BTX injection should pause more than three months from last application (Jankovic et al.; 1990 and 2004).

Besides clinical improvement of dystonic symptoms, functional imaging (Ceballos-Baumann et al., 1997; Dresel et al., 2006) and diffusion tensor imaging studies (Blood et al., 2006) in focal forms of dystonia suggested botulinum toxin to have an effect on specific abnormalities in cortical activation patterns and changes in subcortical microstructure .

1.1.3 Imaging approaches in dystonia

Several imaging techniques have been applied to explore the pathophysiology of primary dystonia, such as examination of the white matter by diffusion tensor imaging (DTI) (Carbon et al., 2004; Colosimo et al., 2005; Blood et al., 2006; Bonilha et al., 2007 and 2009) and gray matter analysis by voxel- based morphometry (VBM) (Draganski et al., 2003; Garraux et al., 2004; Etgen et al. 2006; Delmaire et al., 2007; Egger et al., 2007; Obermann et al., 2007), functional receptor binding studies with SPECT (Hierholzer et al., 1994; Perlmutter et al., 1997; Horstink et al., 1997; Naumann et al., 1998) and functional approaches with PET (Ceballos-Baumann et al., 1995; Feiwell et al., 1999; Ibáñez et al., 1999) and fMRI (Peller et al., 2006; Dresel et al., 2006).

But functional imaging data about cranial forms are still sparse. A previous fMRI study suggested abnormal somatosensory cortex activation in patients with blepharospasm and Meige's syndrome during a motor task as a common abnormality in orofacial dystonia (Dresel et al., 2006). This finding drew the attention closer to the evaluation of somatosensory information processing in orofacial dystonia regarding somatosensory cortex responses to sensory stimulation.

1.2 Functional magnetic resonance imaging (fMRI)

FMRI offers a low risk, non-invasive method to study functional processes in the human brain by mapping biological and physiologic parameters in vivo.

Fusion of functional and high resolution imaging data allows the cartography and identification of cortical responses to external stimuli delivered to the brain. The most common fMRI method is based on detection of blood oxygen level dependent (BOLD) signal changes caused by the task related adjustments of hemodynamic and metabolic demands in neuronal active tissue (Logothetis and Pfeuffer 2004).

With constant improvement in MRI scanner and image acquisition techniques, and progress in statistical analysis, fMRI became the most dominant and fastest expanding method among brain researchers (Logothetis 2008). FMRI has a wide range of application in various research approaches on physiological and pathological conditions of the human brain or brain areas, e.g. the motor or somatosensory cortex.

1.2.1 Biological background of fMRI: The BOLD effect

Local signal intensity changes based on the blood oxygenation level dependent (BOLD) contrast provide an indirect marker for neuronal activity and allow the detection and identification of differences in brain activity.

Different susceptibility characteristics of paramagnetic deoxyhemoglobin and diamagnetic oxyhemoglobin serve as an "endogenous contrast agent". They enable real time in vivo mapping of task-related changes in cerebral blood oxygenation and have basic impact on local magnetic field homogeneities and recorded signal strengths (Ogawa et al., 1990).

On the one hand increasing deoxyhemoglobin due to decreasing oxyhemoglobin levels leads to a signal decrease. On the other hand decrease of deoxyhemoglobin or increase of oxygenated hemoglobin result in a signal increase (Ogawa et al., 1990).

Detected signal changes are analyzed by means of the hemodynamic response function, which is an estimated model of the BOLD contrast with a characteristical time course. It starts with the initial dip, supposedly caused by a higher oxygen extraction in neuronal active tissues, and an increase in deoxygenated hemoglobin. The initial dip is discussed controversially, since it was indeed observed in many optical imaging (Malonek et al., 1996 and 1997; Vanzetta et al., 1999; Thompson et al., 2003) and fMRI studies (Menon et al., 1995; Hu et al., 1997; Logothetis et al., 1999; Kim et al., 2000), but also failed to be detected in some other studies (Marota et al., 1999; Silva et al., 2000; Buxton et al., 2001).

With an approximately two second delay, the initial dip is followed by an increase in local blood flow leading to a surplus of oxygenated blood to ensure sufficient neuronal oxygen and glucose supply (Fox et al., 1986 and 1988).

According to the balloon model, increased blood flow leads to fast elastic vessel response with relaxation of venous blood capillaries and thus creates an enlargement in the local blood pool (Buxton et al., 1998; Mandeville et al., 1999; Friston et al., 2000). With growing supply of oxygenated blood the BOLD signal encounters a large increase above baseline. It reaches a maximum after six to ten seconds and merges into a decline of similar length corresponding to the ebbing oxygen oversupply (Buxton et al., 1998; Heeger and Ress, 2002).

Eventually an undershoot below baseline may occur due to a mismatch of still elevated tissue oxygen extraction and again normalized blood flow (Sarty, 2007).

The underlying mechanisms for this characteristic blood flow response are still under discussion. Theories of higher glucose and oxygen consumption and particular increase in local blood flow, based on increasing neuronal and synaptic activity with higher firing rates (Davis et al., 1998; Sibson et al., 1998; Shulman et al., 1998; Hoge et al., 1999), compete with the idea of increasing energy and oxygen demands in astrocytes needed for the clearance of glutamate or the preparation of lactate (Magistretti and Pellerin, 1999).

In addition to the described intrinsic factors such as neuronal activity, blood oxygenation, blood flow and volume, the hemodynamic response depends on extrinsic factors such as fMRI acquisition techniques, experimental paradigms and procedures in data analysis (Heger and Ress, 2002; Nair, 2005).

Especially the experimental paradigm and the post experimental statistical data processing have to be considered carefully, since the BOLD signal is caused by local field inhomogeneities of only two to four percent regarding the overall magnetization (Ogawa et al., 1993, Bandettini et al., 1994).

In summary the BOLD effect can be described as the ability of hemoglobin to create an MRI contrast depending on its oxygenation level (Ogawa et al., 1990).

1.2.2 Image acquisition in fMRI: Echo planar imaging (EPI)

EPI surpasses conventional imaging speed by far and allows to receive a complete brain scan from just one set of acquired data in one to four seconds (Constable and Spencer 2001). This is made possible due to application of strong magnetic gradients enabling a reduction in encoding and readout times. The additional use of oscillating sequential readout and phase encoding gradients further boost the acquisition speed, but do so at the expense of anatomical resolution.

Commonly applied gradient echo sequences in EPI are very sensitive to susceptibility artefacts caused by local field inhomogeneities and are thus extremely capable for the detection of BOLD signals. Further use of modified flip angles cause lesser disturbances in the magnetic equilibrium and enable shorter relaxation and repetition times without big signal deprivation (Cohen, 1999)

1.3 The somatosensory system

The somatosensory system is differentiated into three general sensory modalities: The exteroception or haptic sense, responsible for the sensory perception of the body surface, the proprioception, in charge of the musculoskeletal system, and the enteroception supplying the inner organs (Schmidt and Schaible, 2006).

1.3.1 Physiology of tactile perception

The haptic sense is essential for the recognition of objects and the development of a spatial sense. Haptic stimuli are detected in the hairy and glabrous skin and forwarded by myelinated Aβ afferences to the first neuronal population located in the spinal ganglion. The axons of the first neuron continue along the dorsal column and the medial lemniscal pathway. They pass the fasciculus cuneatus and gracilis and end in the lower medulla oblongata reaching the second neuronal population represented by the nuclei cuneatus and gracilis. Their axons cross as medial lemniscus to the opposite side and synapse at the ventral posterolateral thalamic nucleus.

Incoming trigeminal nerve afferences host their first neuronal population in the trigeminal ganglion and their second neuron in the nucleus principalis before joining the medial lemniscus.

The ascending third neuronal axons reach the fourth neuronal population located in primary somatosensory cortex via the posterior limb of the internal capsule (Schmidt and Schaible, 2006; Trepel, 2008).

1.3.2 Cortical processing of tactile information

The primary somatosensory cortex is anatomically located in the parietal lobe and embedded in the area between the central and postcentral sulcus. The medial border is the longitudinal fissure and the lateral border the Sylvian fissure. It includes the Brodmann areas 1, 2 and 3 with each area specialized on a certain modality. Brodmann area 1 is mainly in charge of haptic afferences, whereas area 2 is responsible for the sensory integration of limb position. Area 3a receives primarily input from neuromuscular spindles and area 3b particularly maintains information from temperature and pain receptors (Schmidt and Schaible 2006).

The primary somatosensory cortex detects the localization of stimuli as well as their intensity. Similar to the primary motor cortex, it shows a somatotopic organization with a disproportionate cortical representation for the benefit of body areas hosting high peripheral receptor concentrations.

Primary somatosensory cortex efferences reach the thalamus, the sensory trigeminal nuclei, the dorsal column and the posterior horn of the spinal cord. They are able to modulate afferent stimuli awareness.

The secondary somatosensory cortex is located mostly in the parietal operculum along the upper bank of the Sylvian fissure, mainly in the non predominant right hemisphere, and includes parts of the Brodmann areas 40 and 43. Further somatosensory associated areas including Brodmann areas 5 and 7 are located in the posterior parietal cortex and sometimes referred to as tertiary somatosensory cortex.

Its function is to integrate incoming primary sensory cortex information as well as information from primary auditory, visual, vestibular and proprioceptive areas. It thus plays a crucial role for the orientation in three-dimensional space. According to the primary somatosensory cortex it shows a somatotopic structure and has efferences to motor areas (Schmidt and Schaible, 2006; Trepel, 2008).

1.3.3 The somatosensory system and dystonia

Somatosensory cortex alterations had previously been discussed as a primary contributor to the pathogenesis of dystonia (Hallett et al., 1995). This theory found further support by confirmation of a positive correlation between symptom severity and primary somatosensory overactivity in patients with writer's cramp (Lerner et al., 2004).

Another clinical fact underlining the importance of the somatosensory system is the alleviation of dystonic symptoms by sensory tricks, which is mainly described in e.g. cervical dystonia (Fahn, 1988, Filipović et al. 2004).

Similarly, patients with Blepharospasm can improve their eyelid spasms by touching their face (Hallett 2002). The underlying physiology of sensory tricks is yet unknown, but a PET study reported a functional correlate after such a maneuver in cortical sensory and motor areas in cervical dystonia (Naumann et al., 2000).

With the somatosensory system getting more and more in the center of attention in the discussion of the underlying pathologies in focal dystonia, we were interested in the examination of cortical somatosensory response patterns to passive tactile stimulations in orofacial dystonia.

1.4 Devices for sensory stimulation during fMRI

Stimulation devices used in the high magnetic field of MRI scanners have to cope with special safety standards and the geometric limitedness of the scanner gantry. They must operate safely and refrain from causing any imaging artefacts. To cause a feeling of touch or vibration to a subject stimulations can be given by vibrotactile (Gelnar et al. 1998; Golaszewski et al. 2002; Briggs et al. 2004; Gizewski et al. 2005), magneto mechanical (Graham et al. 2001), piezoceramic (Maldjian et al. 1999; Francis et al. 2000; Harrington et al. 2000), pneumatical (Servos et al. 1999; Stippich et al. 1999; Zappe et al. 2004; Wienbruch et al. 2006; Huang and Sereno 2007) or mechanical (Dresel et al. 2008) devices.

Further electrical stimulation techniques were used for sensory stimulation during fMRI experiments (Disbrow et al. 1998; Kurth et al. 1998; Kampe et al. 2000; Ruben et al. 2001; Trulsson et al. 2001; Krause et al. 2001; Del Gratta et al. 2002; Deuchert et al. 2002; Blankenburg et al. 2003; Arthurs et al. 2004).

Electrical stimulation techniques, however, can unintentionally stimulate pain fibers or lead to interferences with the magnetic field of the MRI scanner and corrupt the image quality. Further electrical stimulation showed the biggest intrasubject variances in perception of stimuli compared to thermal or tactile stimulation approaches (Park et al., 2001). Piezoceramic devices work commonly at small vibrational amplitudes and high stimulation frequencies of more than 150 Hz (Francis et al., 2000; Gizewski et al., 2005; Harrington et al., 2000; Maldjian et al., 1999). Their customization is difficult and a permanent stimulation intensity cannot be guaranteed throughout an entire experiment (Harrington et al., 2000).

During fMRI experiments electrically operating devices are limited to the application of stimuli outside the scanner coil.

Pneumatically driven devices, however, allow stimulations of the face, but unlike the mechanical devices, do not physiologically address tactile mechanoreceptors in the glabrous skin (Johansson and Vallbo, 1979).

1.5 This study's goal

Neuroimaging studies previously reported abnormal cortical activation patterns in patients with focal forms of dystonia during sensory and motor tasks. Whereas most studies focused on focal hand dystonia, data about Blepharospasm and Meige's syndrome are lacking.

Using functional magnetic resonance imaging we intended to map and compare somatosensory cortex responses to tactile stimuli, applied by a recently introduced fully automated stimulation device (Dresel et al., 2008), in patients with orofacial dystonia and healthy controls.

We tended to detect differences in cortical somatosensory responses to tactile stimulation in patients. FMRI mapping of abnormal somatosensory cortex activation could help to understand the importance of a defective somatosensory system in the pathogenesis of orofacial dystonia.

In the course of botulinum toxin treatment patients were scanned twice in order to detect a possible treatment effect on somatosensory activation patterns in orofacial dystonia.

2.1 Subjects

In this study we studied 16 patients with idiopathic forms of orofacial dystonia with a mean disease duration of 7 ± 4 years, four of them with blepharospasm and 12 with Meige's syndrome, as well as 15 healthy controls. The mean age in patients was 59.8 (SD ± 6.7, range 48-70, three men and 13 women) and 56.8 years in controls (SD ± 6.6, range 48-66, five men and ten women).

Patients were scanned twice before and four weeks after periorbital injections of botulinum toxin (BTX; mean dose rate of 185 ± 66 units Dysport® or equivalent), when the treatment effect has reached its maximum (Gilio et al., 2000; Colosimo et al., 2003).

Inclusion criteria for all subjects were right-handedness according to the Edinburgh handedness inventory (Oldfield, 1971), a normal anatomic MRI brain scan, no previous brain insult, such as craniocerebral injuries, stroke or central nervous system infection, no malignant neoplasm, no metabolic disease, no previous neuroleptic treatment, no psychiatric or additional neurologic disease and a maximum age of 70.

Participants were informed about the experimental setup, safety instructions and their rights according to the Declaration of Helsinki. All participants gave their written informed consent. The study protocol was approved by the ethics board of the Klinikum rechts der Isar, Technische Universität München.

2.2 FMRI sequence

In this study we used a T2*-weighted echoplanar sequence (TR=2.48 s, TE=50 ms, 28 slices with 10% gap, FoV=224 mm, flip angle 90°, matrix 64×64, voxel size 3.5×3.5×4.5 mm^3, 3 runs a 272 scans with a total scan time of 34 minutes) on a 1.5 Tesla-Siemens Symphony MR scanner (Erlangen, Germany) with an eight- channel- head coil.

After the experiment a high resolution three dimensional T1-weighted MPRAGE image (TR=1.52 s, TE=3.93 ms, TI=800 ms, flip angle 15°, matrix 256×256, FoV=250 mm, 160 slices, voxel size 1×1×1 mm^3) was obtained from each subject for further data processing.

2.3 Tactile stimulation device and experimental setup

In our study we used the fully automated, pneumatically driven tactile stimulation device described in Dresel et al., 2008. The stimulation device enables precisely defined stimulations regarding stimulus length, force and frequency of six skin areas using von Frey-filaments as stimulators. Von Frey-filaments (Optihair22-set, Marstock nervtest, Germany)

are flexible synthetic fibers and guarantee constant force during application of stimuli according to Euler's law of buckling (Fruhstorfer et al., 2001). Von Frey filaments (VHF) enable logarithmically- scaled stimulation forces between 0.25 and 728 Millinewton (mN) and are commonly used for quantitative sensory testing in neurophysiological studies (Yarnitsky, 1997, Park et al., 2001; Rolke et al., 2006;). To avoid nociceptor activation and to optimize contact to the skin area to be stimulated, von Frey hairs are designed to have a dull rounded tip of 0,5 mm in diameter (Rolke et al., 2006).

Stimulations were applied symmetrically to both sides of the forehead with 32 millinewton (mN) filaments, upper lip with 22.6 mN filaments and the back of the hands with 45.3 mN filaments.

Stronger intensities were chosen for the hands, since sensory testing parameters vary depending on the body region with lower thresholds for the face in comparison to the hands (Rolke et al., 2006).

The VFF were attached to mobile pistons of the six pneumatically driven cylinders. Multiple flexible elements allowed exact and individual positioning of the pistons and were attached to a positioning unit. This unit was firmly connected to a mounting rail fixed to the MRI scanner table.

The stimulation device was controlled by the software presentation (http://www.neurobs.com) on a windows-based computer outside the scanner room. This computer was connected to a signal converter, from which an electromagnetically shielded cable transmitted the actuation signal to the driving unit of the stimulation device. Further a trigger unit was used to synchronize the application of stimuli with the MRI time series. The driving unit was situated underneath the scanner table and was connected to a pressurized air supply outside the scanner room delivering 5-6 bar pressurized air.

Photos were taken at times to document the experimental setup and subjects' positioning.

In comparison to other stimulation devices presented in the introduction, the device used in this study allowed a very physiological way of tactile stimulation at a high spatial and temporal accuracy and enabled safe stimulation without causing artefacts inside the scanner coil.

After safety instructions and briefing, subjects were positioned on the scanner table and the stimulation device was adjusted. Hands were placed on a foam pillow in a way that allowed the von Frey- filaments to touch the skin perpendicularly. Two belts additionally supported

the arms to ensure a comfortable fixation in order to maintain adjustments and avoid involuntary motor activity. Two foam pads were attached to the subject's head within the scanner coil in order to minimize movement artefacts by head motion.

2.4 Stimulation paradigm

During the experiment a series of stimulation delivered to one body area at a time consisted of eight consecutive applications of stimuli and was delivered at a frequency of four Hertz (stimulation ON for 80 milliseconds, OFF for 170 milliseconds). Each of the six areas was stimulated eight times during each of the three runs and in total 24 times throughout the entire experiment.

The pseudorandomized paradigm allowed only a maximum of four subsequent stimulation series in one area and was designed to start the following task after an alternating interstimulus interval of 7 to 15 seconds.

Log files containing information about the chronology and types of stimulus application were used for post-experimental data analysis.

2.5 Data processing and statistical analysis

2.5.1 Preprocessing of fMRI data

Data analysis was performed on Linux based computers with Matlab 6.5 (The MathWorks, Inc. Natick, MA, USA) and SPM2 (http://www.fil.ion.ucl.ac.uk).

Data were converted into a SPM conform ANALYZE format (Mayo Clinic, Rochester, USA) creating two types of files, an image file and a header file containing information about the image file regarding image and voxel size, as well as the image matrix.

Further a Matlab conform mat file was created during a reorientation step. It contains millimeter based coordinates transferred from the voxel based image coordinates. This transformation is necessary for the alignment of functional with imaging data described in the following steps.

The first two of the overall 270 acquired images in addition to the two dummy scans omitted by the scanner were discarded for each run in order to minimize artefacts caused by transients of the magnetic scanner field.

Subsequent statistical analysis is based on the assumption that voxels are spatially constant over the time series during the fMRI experiment. Head motion induces motion but not task

related signal intensity changes and interactions at voxel level leading to misalignments and consecutive reduction of statistical sensitivity (Hajnal et al., 1994). A six parameter rigid body transformation based on the least squares approach was performed to realign each image of a time series to its first image regarding linear translations and rotational head movements (Friston et al., 1995). This realignment step enabled best possible image alignment before performing statistical tests.

Further a mean image was created during the realignment step. It was later used as target image for the coregistration and as source image for the spatial normalization.

Coregistration was used to align functional with structural data.

Spatial normalization was performed to adjust a subject's individual anatomy onto a standard stereotactic space and to allow signal averaging across subjects (Ashburner and Friston, 2003). This procedure ensures distinctive anatomical structures to have the same coordinates and enables comparison between individual and between- group data. To do so images were normalized to a template based on the Montreal Neurological Institute coordinates (MNI).

In the following smoothing process we applied a Gaussian filter kernel of 8mm Full Width at Half Maximum (FWHM) in order to increase the signal-to-noise ratio (SNR). This step enhanced coherent task-induced signals and averaged out non-coherent noise. It improved further the merging of functional data to a standardized anatomical map by minimizing individual anatomical features.

2.5.2 SPM2 data analysis

After preprocessing, a general linear model (GLM) as implemented in SPM2 was applied to analyze neuroimaging data by statistical parametric mapping. Statistical parametric mapping tested signal intensity changes for their task related specificity at voxel level using t-tests (Friston et al., 1995b).

Obtained results were integrated into an image and interpreted in the context of a normal distribution. Improbable appearances of regional activations were interpreted as experimental effects and task induced responses. Significant areas were projected onto a standard brain MNI format offering three views in coronary, transversal and sagittal plane (Friston et al., 1995b).

An experimental design matrix was generated in first- level analysis for each subject based on the log files recorded during the fMRI experiment.

Each series of stimuli were modeled as a single condition using a stick function encoding the onsets of each trial to be convolved with the hemodynamic response function in order to deliver the regressor in the design matrix. Thus contrasts between the active conditions, e.g. stimulation of the face, lip or hand, and rest were created, and a specific model was estimated based on the activation-rest contrasted images using one sample t-tests .

To eliminate nuisance variables such as physical and physiological low frequency artefacts based on scanner drift-, cardiac- or respiratory artefacts (Friston 2003), a 320 s high-pass filter was applied.

Random effects analysis was performed in second- level analysis to allow valid inferences for the population from which the sample was drawn (Penny and Holmes, 2003).

To evaluate between-group differences in patients before treatment with botulinum toxin and controls we selected a two sample t- test. For the comparison of patients before and after treatment we applied a paired t-test.

T- and F- contrasts between the groups were created for the estimated models and the results of the statistical analysis were explored and characterized interactively on an MNI overlay map.

To evaluate statistical significance of each stimulation type a statistical threshold of $p<0.001$ uncorrected was chosen to show task related activations to be significant.

Activations were anatomically located and confirmed on a canonical MNI image. In addition, MNI coordinates of activation maxima were converted into Tailarach space (Talairach and Tournoux, 1988) using the method suggested by Matthew Brett (http://www.mrc-cbu.cam.ac.uk/Imaging/MniTalairach) to identify the corresponding Brodmann areas.

2.6 Behavioral data

2.6.1 Sensory and pain perception thresholds

Before the actual fMRI experiment, subjects underwent evaluation of their individual sensory and pain perception thresholds in all six areas to be stimulated during the experiment according to the method of limits (Yarnitsky, 1997).

For the detection of the sensory and pain thresholds subjects were asked to keep their eyes shut and to concentrate on stimulations while logarithmically scaled von Frey-filaments

(VFF) were applied with ascending and descending stimulation intensities. The stimulation intensity which induced in at least 50% of stimulations a sensation of touch or respectively pain defined the corresponding threshold.

Data were recorded for statistical ANOVA comparison of sensory and pain thresholds between patients vs. controls and patients before vs. after treatment with botulinum toxin using SPSS 14 (SPSS, Chicago, IL).

2.6.2 Post- fMRI questionnaire

Good concentration on stimuli during the fMRI experiment was important, since individual attention (Arthurs et al., 2004; Hämäläinen et al., 2000; Hoechstetter et al., 2000) and anticipation (Carlsson et al., 2000; Porro et al., 2004) were shown to modulate activations in sensory fMRI studies. To achieve best possible concentration on applied stimuli a post-experimental questionnaire was announced prior to the fMRI experiment.

Detailed information about the questionnaire was concealed in order to prevent individuals from focusing too much on questionnaire details. Participants were asked to refrain from counting the applied stimulations or from evaluating the stimulation frequency.

The questionnaire focused on perceived stimulation intensity and its change throughout the fMRI experiment. Further subjects were asked whether the location of applied stimuli changed or any unpleasant or painful sensation, as well as noise generated by the stimulation device during application of stimuli, was perceived. The appearance of the latter was important, since simultaneous noise during stimulation application would mean an additional unintended task- associated acoustic input.

Subjects classified stimulation intensities perceived during the experiment on an analogue scale with a range from 0 (no stimulation perceived) to 10 (strongest, but not painful or unpleasant stimulation). Data were statistically analyzed using an ANOVA test on SPSS 14 (SPSS, Chicago, IL) to evaluate significant between group differences in perception of stimulation intensities during the fMRI experiment.

2.6.3 Clinical assessment scales

Five clinical scores were collected to document the patient's condition on the day of the experiment and to keep record about the long- term development of the disease under treatment with botulinum toxin. In addition to the Jankovic (Jancovic et al., 1990) and Elston score (Elston 1992) which are specific clinical scores for orofacial dystonia, the appropriate items of the Fahn- Marsden rating scale (F-M) (Burke et al., 1985), the Unified Dystonia Rating Scale (UDRS) (Comella et al., 2003) and the Global Dystonia Rating Scale (GDS) (Comella et al., 2003) were used.

The Fahn- Marsden rating scale generally reflects situational symptom appearance and the individually experienced discomfort. It consists of a provoking, a severity and a weighting factor (Burke et al., 1985). The provoking factor with a range from 0-4 is multiplied by the severity factor with equal range. Depending on the examined area a weighting factor of 0,5 for eyes and mouth, and a factor of 1 for speech and swallowing is applied. Acquired values are added up to a possible maximum of 32 points.

The UDRS delivers ratings of three cranial areas such as motor severity in eyes and upper face, lower face, jaw and tongue and is added to a duration factor (Comella et al., 2003). The UDRS rates the intensity of symptoms regarding severity and duration of dystonic symptoms at rest or in association with defined motor action. Patients can reach an overall score from 0 to 16 points.

In the global dystonia rating scale ten body areas, three of them of interest for this study, are rated by an examiner (Comella et al., 2003). Scores reach from 0 to 10 regarding the severity of the affected eyes/upper face, lower face, jaws and tongue. Obtained data are added up to a possible maximum of 30 points in the current study.

The Jankovic blepharospasm scale evaluates the individually experienced severity and frequency of dystonic symptoms during the last three days. Symptom severity and frequency can be totaled to a maximum of 8 points (Jankovic et al., 2009).

The Elston score quantifies the patient's discomfort in his daily routine reaching from functional blindness (1 point) to no reduction in quality of life (6 points) (Elston 1992).

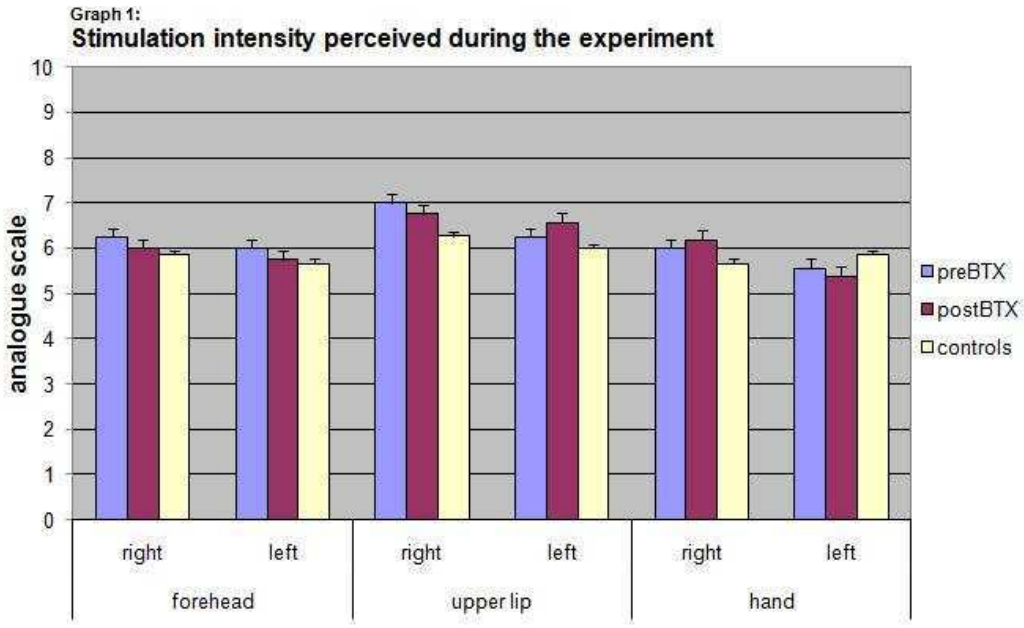
Collected data were statistically analyzed performing paired t- tests on SPSS 14 (SPSS, Chicago, IL) to show significance of score value changes under treatment with botulinum toxin.

3.1 Behavioral data

3.1.1 Behavioral questionnaire

During the fMRI experiment participants experienced all applied stimulations as a normal sensation of touch. ANOVA comparison of perceived stimulation intensities showed no significant between- group differences in patients in comparison to controls and patients before and after treatment with botulinum toxin. No individuals felt an unpleasant sensation induced by the stimulation device such as burning, tickling, itching or sharp pain. Location of applied stimuli did not change throughout the experiments in any case.

All individuals reported good concentration on stimuli throughout the experiment.

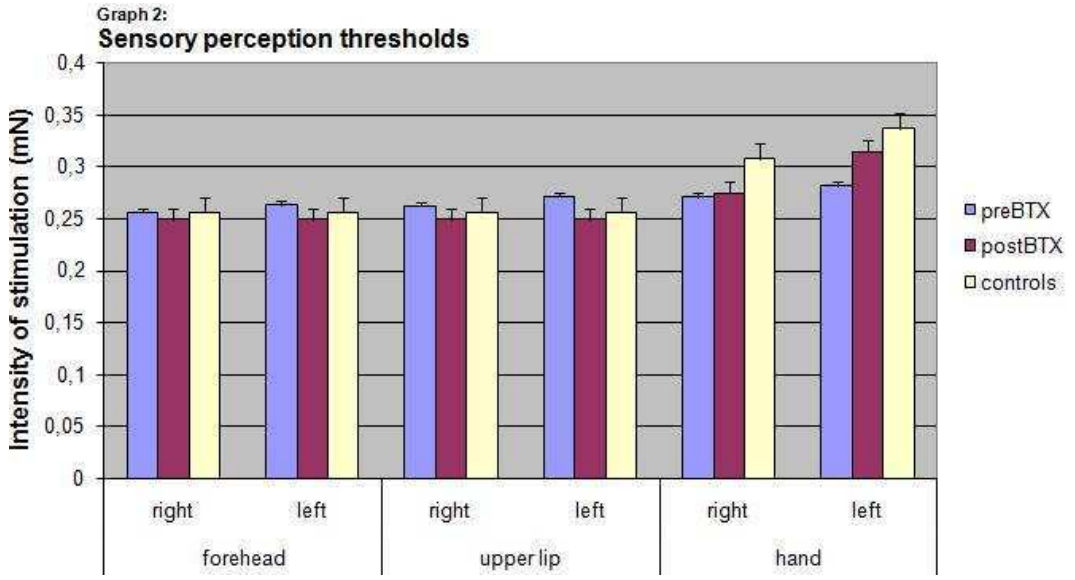


Graph 1 shows mean values of the stimulation intensities perceived during the fMRI experiment in the six different areas denoted in the graph's abscissa for patients before treatment with botulinum toxin (blue), after treatment (red) and controls (yellow). Subjects were asked for the perceived stimulation strength using an analogue scale with range from 0 meaning "no stimulation perceived" to 10 meaning "strongest but non-painful or unpleasant sensation". Error bars indicate the standard error.

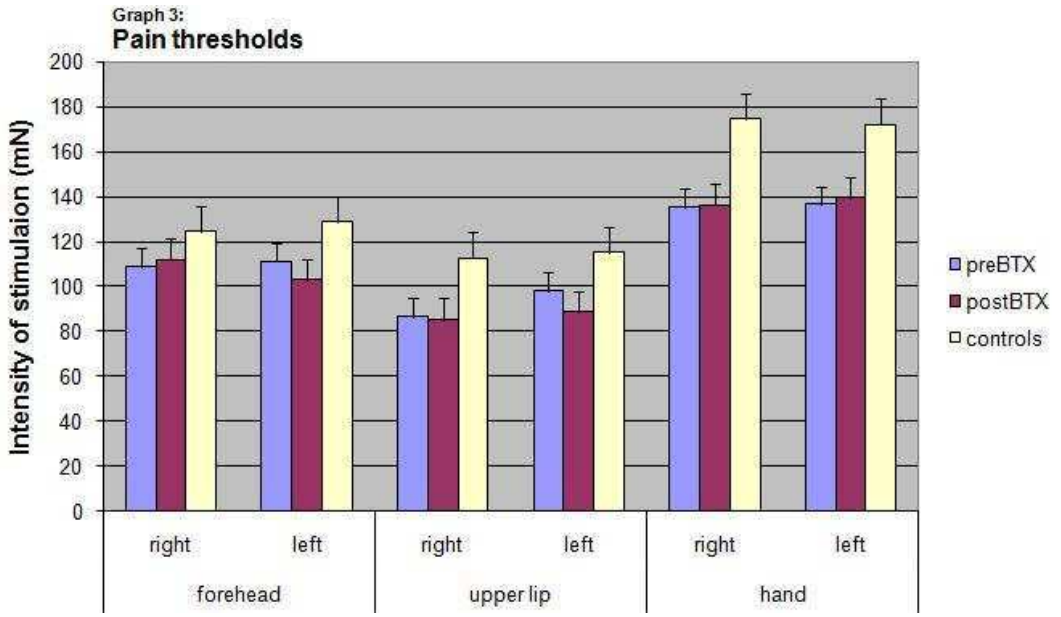
3.1.2 Sensory and pain perception thresholds

ANOVA analysis of data concerning between group differences in mechanical sensory perception and pain thresholds showed no significant overall group differences in any of the six stimulated body areas. Averaged pain thresholds were in general insignificantly higher in

controls. No significant modulation of sensory or pain thresholds was observed in patients under treatment with BTX.



Graphs 2 and 3 show mean values of sensory perception and pain thresholds evaluated with von Frey- filaments in patients before treatment with botulinum toxin (blue), after treatment (red) and controls (yellow). The ordinate displays strength of applied von Frey-filaments in Millinewtons (mN). Error bars indicate the standard error.

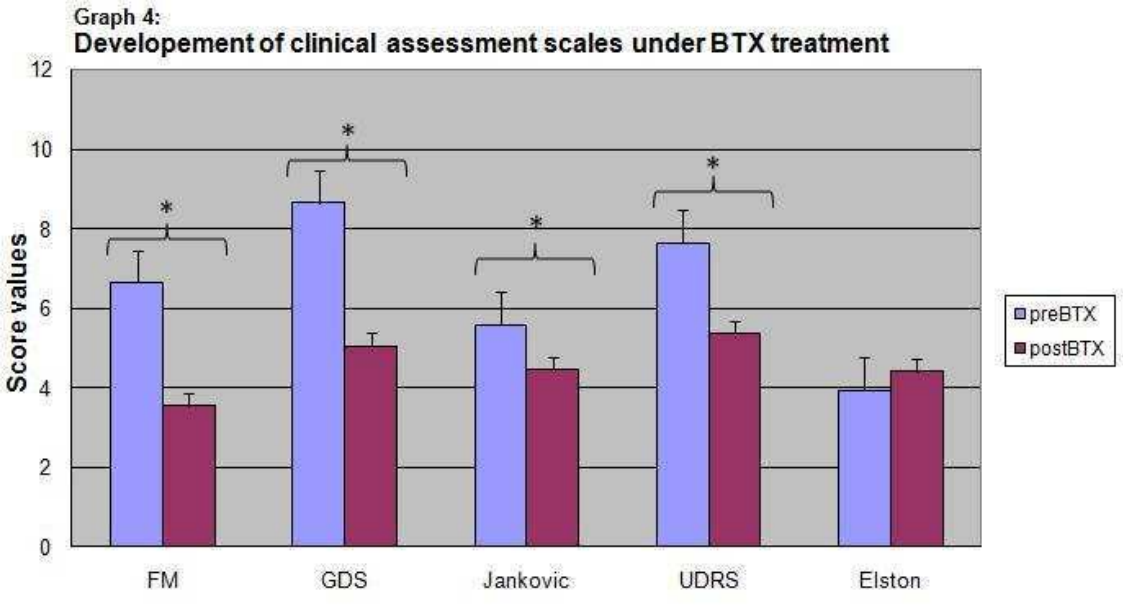


3.1.3 Clinical assessment scales

Paired t-tests were used to compare the scores under treatment with botulinum toxin in all five clinical assessment scales. In order to minimize the occurrence of a Type-I-error a Bonferroni correction was performed which lowered the level of significance from the five percent level ($p<0.05$) to the overall one percent level of significance ($p<0.01$).

Statistically significant symptom improvement was seen in four evaluated scores, the Fahn-Marsden, the Global Dystonia rating scale, the Jancovic Score and the Unified Dystonia Rating Scale.

The Fahn- Marsden rating scale declined from an original value of 6.8 (SD +/- 4.2) to 3.7 points (SD +/- 2.9, $p<0.001$). The Global Dystonia rating scale was reduced from 8.8 (SD +/- 4.5) to 5.2 (SD +/- 3.6, $p<0.001$). The Unified Dystonia Rating Scale lowered from 7.7 (SD +/- 3.4) to 5.4 (SD +/- 2.9, $p<0.001$). In the same manner the Jankovic score decreased from 5.8 (SD +/- 0.9) to 4.6 (SD +/- 1.3, $p=0.001$). The Elston score showed an increase from 3.9 (SD +/- 0.7) to 4.4 (SD +/- 0.7, $p=0.013$). An increase in Elston score indicates a clinical improvement similar to a decrease of FM, GDS, UDRS and Jankovic scores.



Graph 4 shows symptom improvement in patients before (blue) and after treatment with botulinum toxin (red). The ordinate displays the score values. A statistically significant improvement (* $p<0.01$ with Bonferroni correction) was seen in four evaluated scores: The Fahn-Marsden rating scale (FM), the Global Dystonia Rating Scale (GDS), the Jancovic Score and the Unified Dystonia Rating Scale (UDRS). The Elston Score (Elston, $p=0.013$) just failed to reach statistical significance.
Error bars indicate the standard error.

3.2 Within-group analysis of functional data

In this study, the SPM2 within-group analysis focused on the spatial distribution of activation networks in primary and secondary somatosensory cortex at a statistical threshold of $p<0.001$ uncorrected for the different stimulation tasks. Activation of other areas such as the mesial premotor cortex, thalami and basal ganglia during tactile stimulation are reported elsewhere (Dresel et al., 2010). Primary somatosensory cortex response was detected bi- and unilaterally with commonly stronger activation on the contralateral side. It was anatomically located in the postcentral gyrus including Brodmann areas 2 and 3.

The hand area was located medial, superior and posterior to the face representation.

Lip and forehead representation were in close spatial proximity making a differentiation between these areas sometimes difficult. The lip representation was commonly found more superior and medial to the forehead representation. The face representation, particularly the forehead representation, was detected close to the Sylvian fissure and the secondary somatosensory cortex.

Secondary somatosensory cortex activation showed bilaterally active networks with mostly contralateral dominance. It was anatomically located in the postcentral gyrus, inferior parietal lobule, superior temporal gyrus and posterior insula and included the Brodmann areas 5, 40 and 43.

3.2.1 Stimulation of the forehead

Evaluation of the activation induced by stimulation of the forehead displayed contralateral primary somatosensory cortex activation and bilateral activation in secondary somatosensory cortex in controls. It should be further noted that there was also significant ipsilateral primary somatosensory cortex activation found in controls.

Primary and secondary somatosensory cortex activation appeared in a similar pattern in patients.

Table 1:

MNI coordinates of the local activation maxima during tactile stimulation of the forehead in S1 and S2

group	left sided stimulation						right sided stimulation					
	x	y	z	t-level	BA	function	x	y	z	t-level	BA	function
controls	66	-14	32	5,57	3	S1	-62	-24	32	7,19	2	S1
	54	-18	16	9,11	43	S2	-58	-34	22	7,16	40	S2
preBTX	52	-28	20	7,47	40	S1/S2	-64	-18	22	4,46	40	S1
	A clear distinction between S1 and S2 activation was not possible						-56	-18	12	5,88	41	S2
postBTX	66	-16	20	4,92	43	S1	-64	-24	28	4,82	2	S1
	64	-26	20	7.01	40	S2	-54	-22	16	5.9	40	S2

Table 1 shows coordinates of maximum activation in primary (S1) and secondary (S2) somatosensory cortex during stimulation of the forehead. Maxima are given in MNI coordinates and strengths of activations are indicated by t-level values ($p<0.001$ uncorrected). Brodmann areas (BA) were identified by transferring MNI coordinates into Tailarach space.

Fig. 1:

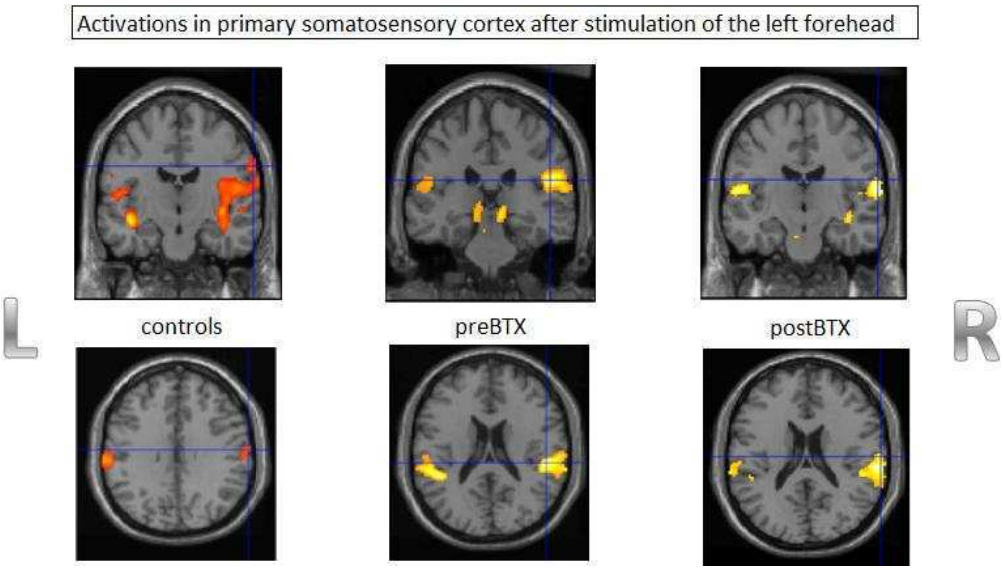


Fig. 1 displays SPMs induced by tactile stimulation of the left forehead in controls and patients before (preBTX) and after (postBTX) treatment with botulinum toxin on coronary and axial slices. The crosshair is centered on the Primary somatosensory cortex maximum activation listed in table 1. Images are given in neurological convention (L=left side, R=right side).

Fig. 2:

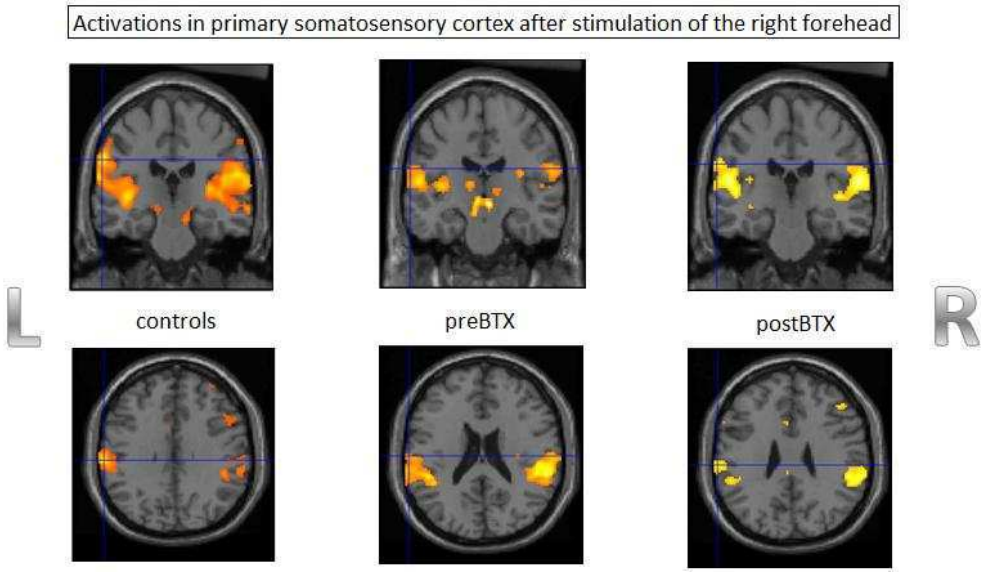


Fig. 2 displays SPMs induced by right forehead stimulation in all three groups on coronary and axial slices.
The crosshair is centered on the S1 maximum activation listed in table 1.

3.2.2 Stimulation of the upper lip

Analysis of the cortical response after stimulation of the upper lip showed contralateral primary and bilateral secondary somatosensory cortex activation in controls. Further there was also significant ipsilateral primary somatosensory cortex activation. The secondary somatosensory cortex activation was in general stronger on the side contralateral to the stimulation.

Primary and secondary somatosensory cortex activation appeared likewise in patients, with the exception of strictly contralateral response in patients postBTX during left sided stimulation.

Table 2:
MNI coordinates of the local activation maxima during tactile stimulation of the upper lip in S1 and S2

group	left sideded stimulation						right sided stimulation					
	x	y	z	t-level	BA	function	x	y	z	t-level	BA	function
controls	66	-18	38	6,27	3	S1	-58	-18	42	8,38	3	S1
	54	-18	16	11,56	43	S2	-62	-24	22	11,77	40	S2
preBTX	50	-30	24	6,86	40	S1	-66	-30	24	5,07	40	S1
	62	-30	20	5,65	40	S2	-50	-18	16	7,37	43	S2
postBTX	56	-22	24	5,74	40	S1	-64	-26	28	5,19	40	S1
	58	-28	22	9,45	40	S2	-56	-22	14	6,5	40	S2

Table 2 displays coordinates of maximum activation in S1 and S2 during stimulation of the upper lip.

Fig. 3:

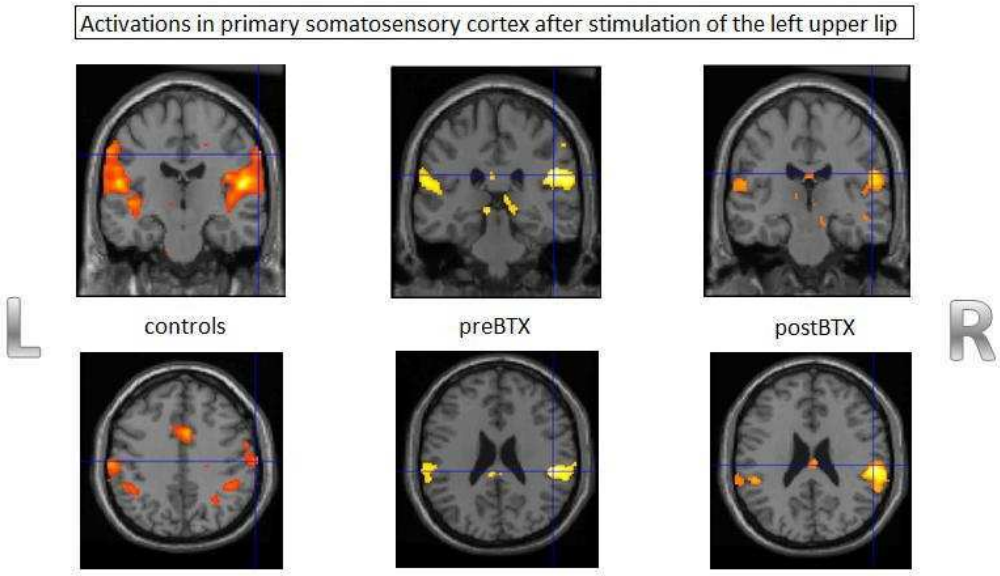


Fig. 3 displays SPMs induced by left upper lip stimulation in all three groups on coronary and axial slices. The crosshair is centered on the maximum S1 activation listed in table 2.

Fig. 4:

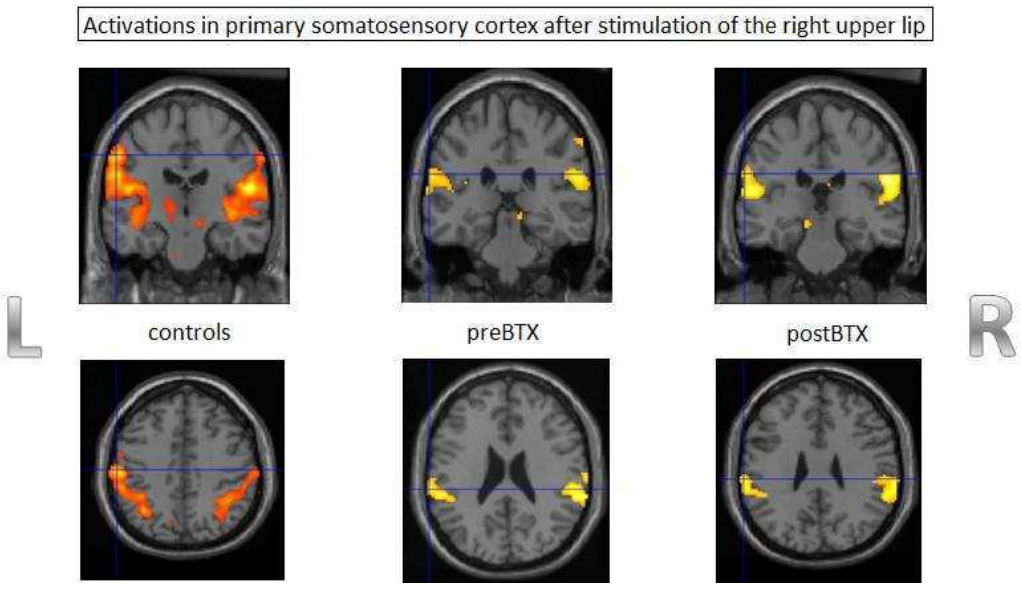


Fig. 4 displays SPMs after right lip stimulation in all three groups on coronary and axial slices. The crosshair is focused on the center of maximum S1 activation listed in table 2.

3.2.3 Stimulation of the hands

Stimulation of the hands led to contralateral response in primary somatosensory cortex and bilateral activation in secondary somatosensory cortex in controls. Significant ipsilateral primary somatosensory cortex activation was only seen during right sided stimulation.

Secondary somatosensory cortex was commonly stronger on the contralateral side of the stimulation.

In patients preBTX primary somatosensory cortex activation was stronger on the contralateral side during left sided- and on the ipsilateral side during right-sided stimulation.

Primary somatosensory cortex activation was seen in patients postBTX during right sided stimulation only.

Secondary somatosensory cortex response showed generally bilateral activation in patients.

Table 3:
MNI coordinates of the local activation maxima during tactile stimulation of the hand in S1 and S2

	left sided stimulation						right sided stimulation					
	x	y	z	t-level	BA	function	x	y	z	t-level	BA	function
controls	68	-26	44	4,64	2	S1	-60	-24	34	8,82	2	S1
	66	-22	20	8,86	40	S2	-62	-30	18	15,16	40	S2
preBTX	60	-28	48	5,78	2	S1	62	-30	48	5,02	2	S1
	62	-34	28	9,32	40	S2	-58	-34	22	12,45	40	S2
postBTX	-	-	-	-	-	-	-58	-32	48	4,65	40	S1
	54	-26	26	7,99	40	S2	-64	-28	28	6,72	40	S2

Table 3 shows coordinates of maximum activation in S1 and S2 during stimulation of the hands.

Fig. 5:

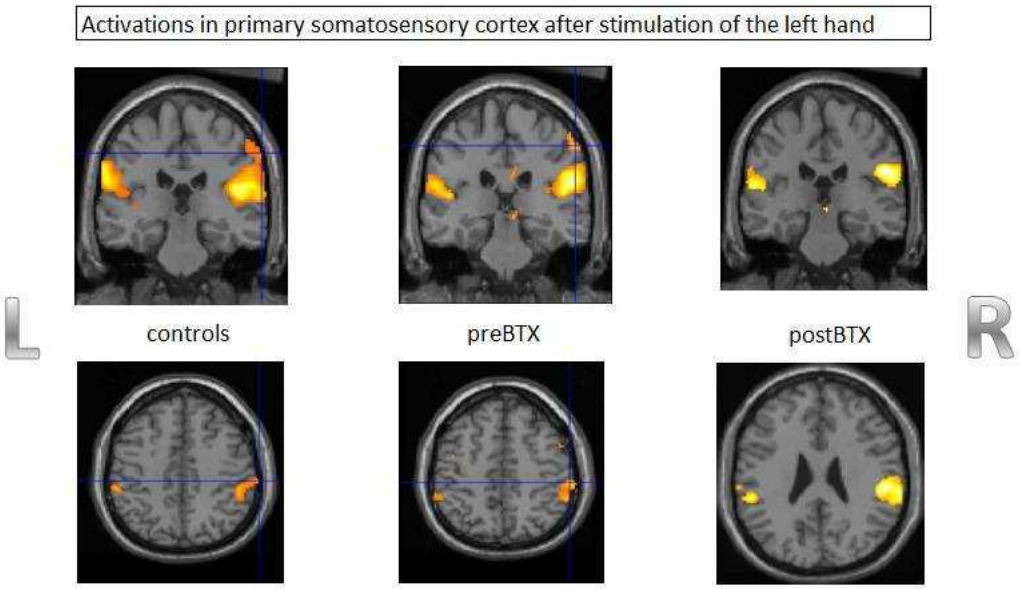


Fig. 5 displays SPMs during left hand stimulation in controls and patients preBTX on coronary and axial slices. No significant S1 activation was detected at the statistical threshold of $p<0.001$ in postBTX group. The crosshair is centered on maximum S1 activation listed in table 3.

Fig. 6:

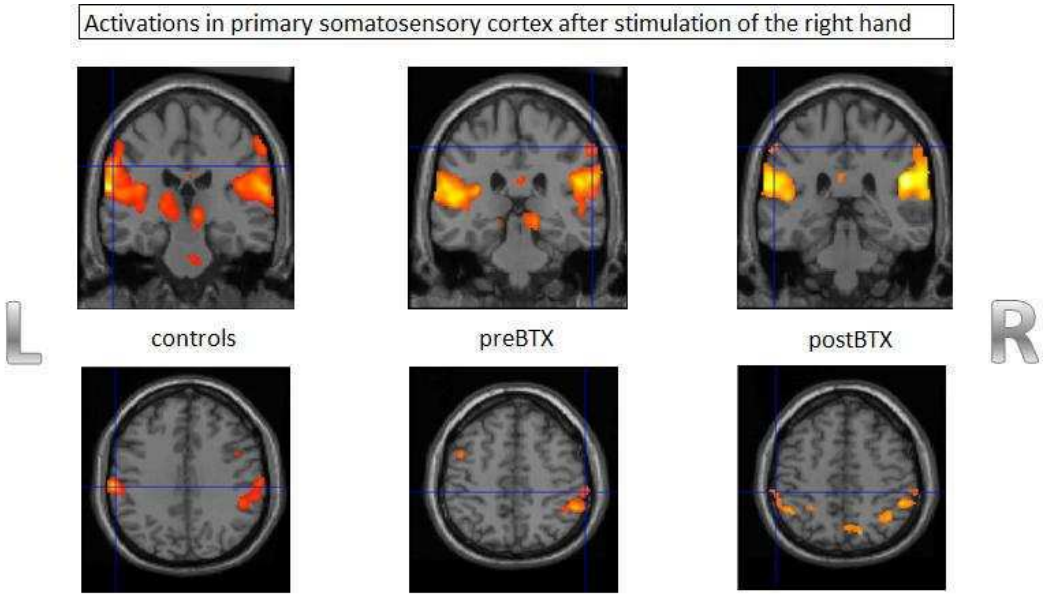


Fig. 6 displays SPMs during right hand stimulation in all groups on coronary and axial slices. S1 response in controls and postBTX group showed mainly contralateral activation, whereas suprathreshold activation in preBTX group was only seen ipsilaterally. The crosshair is focused on the center of maximum S1 activation listed in table 3 above.

Further activations were seen in all three groups in premotor cortices, Broca's area, posterior and anterior insula, middle and superior temporal gyri, as well as cerebellar and thalamic structures.

3.3 Between group comparisons

Between group comparisons were performed to detect differences in primary and secondary somatosensory cortex response to stimulation tasks in patients and controls and to examine the effect of botulinum toxin treatment on sensory activation patterns in patients.

3.3.1 PreBTX vs. Controls

In primary somatosensory cortex patients showed underactivity contralateral as well as ipsilateral to the side of the stimulation in comparison to controls during forehead and lip stimulation as displayed on the SPM below.

Stimulation of the hands led to activation difference during right sided stimulation only. Underactive areas were anatomically situated in postcentral gyrus and identified as Brodmann areas 2 and 3. Patients preBTX showed impaired secondary somatosensory cortex

activation predominantly in right hemispheric Brodmann areas 40 and 43 during stimulation of the face and the right hand.

Primary and secondary somatosensory cortex areas showed no significant overactivity in patients preBTX compared to controls at any time or stimulation task given.

Table 4:
MNI coordinates of detected maxima of underactivity in S1 and S2 in patients preBTX in comparison to controls

left forehead							right forehead						
x	y	z	t-level	area	function	side	x	y	z	t-level	area	function	side
-66	-24	34	4,09	2	S1	ipsi	-58	-24	48	3,5	2	S1	co
64	-18	34	3,47	3	S1	co	66	-16	38	3,28	4	S1	ipsi
54	-20	16	4,22	43	S2	co	58	-22	18	4,54	40	S2	ipsi
left lip							right lip						
x	y	z	t-level	area			x	y	z	t-level	area		
-56	-28	52	3,91	2	S1	ipsi	-54	-20	28	3,61	2	S1	co
66	-16	38	3,33	4	S1	co							
54	-22	14	4,18	40	S2	co	56	-24	16	4,53	40	S2	ipsi
left hand							right hand						
x	y	z	t-level	area			x	y	z	t-level	area		
-	-	-	-	-	-	-	-56	-28	50	3,84	2	S1	co
-	-	-	-	-	-	-	58	-24	18	3,42	40	S2	ipsi

Table 4 displays coordinates of maximum S1 and S2 activation differences in controls and patients preBTX. Maxima are given in MNI coordinates. Significance of activation difference is described by t-values at a statistical threshold of $p<0.001$. Brodmann areas (BA) were defined transferring MNI coordinates into Tailarach space.
Appearances of activations regarding the side of stimulation are abbreviated in the following way: co = contra, ipsi = ipsilateral

Fig.7:

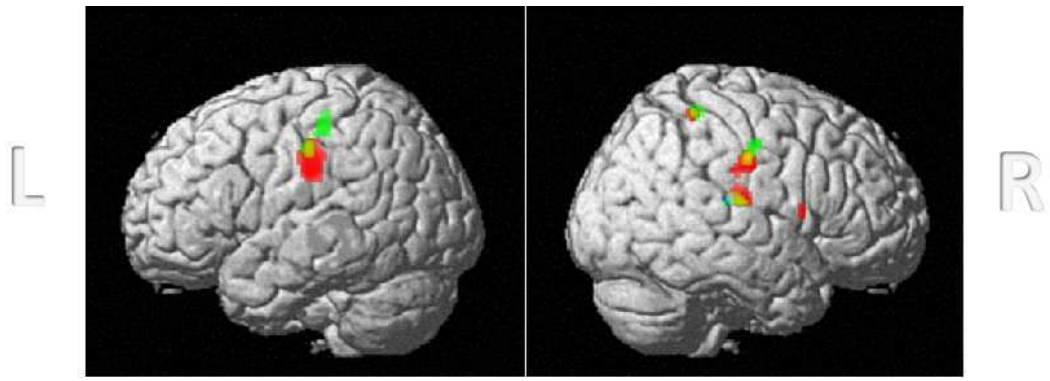


Fig.7 shows SPMs of the between group comparison preBTX vs. controls on a volume rendered standard brain for left-sided stimulation. Displayed areas mark regions of cortical underactivity in the primary and secondary somatosensory cortex in patients during stimulation of the left forehead (red), the left upper lip (green) and the left hand (blue). Yellow areas mark overlap between forehead and lip representation in S1 and S2. Stimulation of the face led to apparently lower somatosensory cortex response in patients, whereas the cluster seize of underactive areas within the somatosensory cortex after right hand stimulation was comparatively small, e.g. S2 activation marked blue in the SPM. Similar results were found for right-sided stimulation.

3.3.2 PreBTX vs. PostBTX

No significant changes in primary and secondary somatosensory cortex activation patterns were detected under treatment with botulinum toxin, whereas patients before treatment showed stronger activation patterns in subcortical structures during stimulation of the forehead. This observation could not be made during stimulation of the upper lip.

Stronger subcortical activation during stimulation of the forehead was located in the contralateral putamina and the bilateral thalami.

Table 5:
MNI coordinates of subcortical differential maxima in patients preBTX > postBTX during forehead stimulation

left sided stimulation						right sided stimulation					
x	y	z	t-level	structure	side	x	y	z	t-level	structure	side
32	-20	0	5,59	putamen	co	22	-11	6	4,01	putamen	co
10	-14	2	5,89	thalamus	bilat	-8	-6	-6	5,3	thalamus	bilat

Table 5 displays coordinates of maximum subcortical activation differences in patients before (preBTX) and after (postBTX) treatment with botulinum toxin. Maxima are given in MNI coordinates. Significance of activation difference is described by t-values at a statistical threshold of $p<0.001$. Subcortical structures were defined transferring MNI coordinates into Tailarach space.
Appearances of activations regarding the side of stimulation are abbreviated in the following way: co = contra, bilat = bilateral

Fig.8:

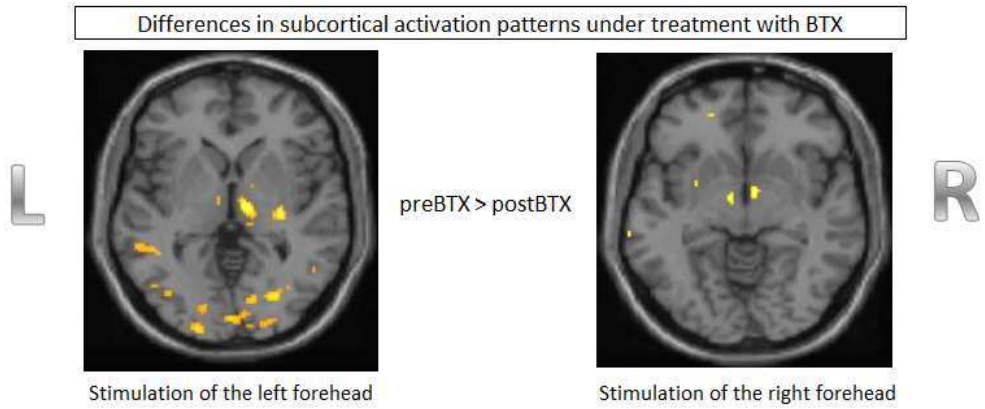


Fig.8 shows SPMs with stronger subcortical activation during stimulation of the forehead in patients before treatment (preBTX) with botulinum toxin in comparison to patients after treatment (postBTX). Activation differences are displayed on axial slices.
Patients preBTX showed stronger activation in the bilateral thalami and the posterior part of the contralateral putamen.
A small cluster can also be seen in the contralateral globus pallidus internus during left sided stimulation.

Between-group comparison of patients before and after treatment with botulinum toxin detected no differences in regard of underactive activation patterns in patients preBTX.

Analysis of the fMRI data showed an abnormal primary and secondary somatosensory cortex response during each facial stimulation task in patients before treatment with botulinum toxin in comparison to controls. Only stimulation of the right hand led to a significant activation difference in primary and secondary somatosensory cortex response in patients preBTX. No effect of botulinum toxin treatment on cortical response to tactile stimuli was detected in primary and secondary somatosensory cortex, whereas the contralateral basal ganglia and bilateral thalami showed stronger activation during stimulation of the forehead in patients preBTX when compared to postBTX.

4.1 Abnormal somatosensory activation patterns after sensory stimulation in dystonia

In comparison to controls we found in this study significantly reduced activation in somatosensory cortex response to tactile stimuli applied to untreated patients' forehead and upper lip, whereas only right sided stimulation of the hand led to contralateral activation decrease in patients' somatosensory cortex.

ANOVA comparison of sensory perception thresholds displayed neither significant differences between patients and controls, nor significant changes in patients after treatment with botulinum toxin.

Thus it is very unlikely that our findings were corrupted by significant between group differences in sensory perception.

Further evaluation of the perceived stimulation strengths after the fMRI experiment showed no significant between group or between task differences and can also be excluded as underlying cause for e.g. the exclusive abnormality in right hand representation.

Currently, there is only one other sensory imaging study on orofacial dystonia in literature which examined the cortical response to one-sided vibratory lip and hand stimulation in patients with Meige's syndrome and Blepharospasm in PET (Feiwell et al., 1999). This study reported vibration-induced decrease in primary somatosensory cortical blood flow response after stimulation of the lower lip, which is in line with our results during stimulation of the face.

Further, although not in a sensory study design, an abnormal somatosensory activation pattern was described in a motor fMRI study examining a whistle task in Meige's syndrome

and Blepharospasm (Dresel et al., 2006). Additionally to specific alterations in premotor and motor activation within the mouth representation area in Meige's syndrome, the study reported enhanced primary somatosensory cortex activation in both forms of orofacial dystonia. The authors postulated a reduction in oromandibular motor activation to be a specific finding in Meige's syndrome and suggested the abnormal somatosensory representation to be a common and independent contributor to the pathogenesis of orofacial dystonia.

Our current fMRI study underlines the importance of a disorder in cortical processing of cutaneous tactile inputs from clinically affected body areas in orofacial dystonia.

However the detection of an abnormal cortical representation of the clinically unaffected right hand indicates a more general dysfunction of the somatosensory cortex.

Based on this finding a general failure in cortical sensory information processing of not only symptomatic, but also asymptomatic body areas has to be suggested for orofacial dystonia, raising the question whether there is a common somatosensory defect contributing to the specific clinical appearances in dystonia.

Therefore, comparisons with functional imaging results in other forms of focal dystonia are helpful.

Focusing on somatosensory responses to sensory tasks, a PET study examined cortical blood flow responses to passive vibrotactile stimulation applied to the hands and lips in diverse forms of idiopathic dystonia and showed significant reduction in somatosensory blood flow in patients (Tempel and Perlmutter 1990).

A subsequent study focused on focal hand dystonia using the same methods for stimulation of both hands and likewise detected a decrease in corresponding contralateral primary somatosensory cortex peak response (Tempel and Perlmutter 1993).

Our study introduced a novel approach to investigate somatosensory information processing in focal dystonia. The tactile stimulation device enabled a so far unknown physiological and highly standardized way of stimulation.

It allowed for the first time the bilateral examination of three body areas in one experiment applying highly standardized physiological stimuli to clinically affected as well as unaffected body areas.

A similar consistency as reported for imaging correlates of dystonic body regions cannot be seen in data regarding cortical response patterns of clinically unaffected body areas.
We observed an activation difference during right hand stimulation in orofacial dystonia.
In a previous PET study, a trend for a reduced blood flow response during stimulation of the clinically unaffected hands had been found in orofacial dystonia (Feiwell et al., 1999).
Other sensory PET studies reported abnormal somatosensory blood flow responses after vibrotactile stimulation of a clinically unaffected hand in focal hand and idiopathic dystonia (Tempel and Perlmutter, 1990 and 1993).
Thus, it is not consistently clear if abnormal somatosensory cortical representation of asymptomatic body areas after vibrotactile or tactile stimulation is a specific feature of non cranial forms or a common finding in different forms of focal dystonia.
In the context of the present data alterations in somatosensory representation of the face seem to be the primary pathological finding in orofacial dystonia, whereas abnormal cortical representation of the clinically unaffected right hand indicates further abnormal brain responses of clinically uninvolved body parts.

4.2 Psychophysical aspects and sensory abnormalities in focal dystonia

In comparison to sensory neuroimaging studies, which examine the correlation between a physical stimulus and its cortical response objectively, psychophysical studies investigate the relationship between a physical stimulus and its subjective perception.
Evaluation of sensory perception thresholds in our study is not comparable to psychophysical studies, but the results from psychophysical studies on haptic stimulation in dystonia, especially orofacial dystonia, are relevant in the discussion of an abnormal somatosensory system in dystonia. Thereby not only findings in dystonic limbs, but also in unaffected body regions should be considered in the context of our finding regarding an abnormal cortical hand representation in orofacial dystonia.
Only one study evaluated temporal discrimination thresholds in Blepharospasm and identified higher values in affected, but also unaffected body areas in comparison to controls and patients with hemifacial spasm (Fiorio et al., 2008). Stimuli were applied to the skin above the orbicularis muscle and the unaffected hands.

Due to the comparison with hemifacial spasm these findings showed clear support for an underlying central dysfunction in Blepharospasm, and demonstrated impaired information processing of clinically unaffected hands in a form of orofacial dystonia.

Further testing of sensory temporal discrimination thresholds in a large sample of patients with diverse forms of focal dystonia, among them blepharospasm, cervical dystonia, and focal hand dystonia, demonstrated abnormalities in clinically affected and all unaffected areas when stimuli were applied to an area near the orbita, index finger and neck (Scontrini et al., 2009). In comparison to controls and patients with hemifacial spasm the authors concluded altered somatosensory temporal discrimination thresholds in asymptomatic areas to be a general characteristic trait for primary focal dystonia and postulated these findings to be suitable for the screening of subclinical forms.

Abnormalities in temporal discrimination thresholds were also reported for genetically determined dystonia in clinically unaffected DYT1 carriers (Fiori et al., 2007) as well as abnormalities in spatial discrimination thresholds in asymptomatic relatives (O'Dwyer et al., 2005). Latter findings were further discussed as a characteristic endophenotype and possible precondition for the future development of dystonia.

Synopsis of the described sensory abnormalities in dystonia in comparison to normal findings in hemifacial spasm and controls, as well as the abnormal cortical responses to peripheral sensory stimulation seen in functional imaging studies, suggest dystonia to be a primary disease of the central nerve system.

4.3 Pathophysiological model of an abnormal somatosensory system in dystonia

In an effort to understand the central pathology causing the clinical characteristics in focal dystonia two theories were drawn from electrophysioligical and functional imaging studies: The concepts of a deficient center surround inhibition e.g. in thalamostriatal pathways, basal ganglia and somatosensory cortex curcuits, as well as the theory of an abnormal cortical plasticity of the dystonic brain.

Deficient center surround inhibition was used to explain abnormalities of the motor cortex shown in transcranial magnetic stimulation (Ridding et al., 1995; Ikoma et al., 1996; Chen et al., 1997; Curra et al., 2000; Sohn et al., 2004) and functional imaging studies (Ceballos-

Baumann et al., 1995 and 1997; Ibanez et al., 1999; Dresel et al., 2006, Haslinger et al., 2010), but could also apply for the discussion of abnormal findings in the sensory system.

As known from electrophysiological studies somatosensory- evoked potentials (SEP) show with ongoing stimulation a physiological SEP- amplitude decrease in animal models and humans implying an inhibition essential for temporal discrimination of sequential stimuli and their contrasting (Angel 1967, Shagass and Schwartz 1964, Wiederholt 1978).

This mechanism is believed to be defective in focal dystonia with improper inhibition resulting in abnormal interpretation of peripheral sensory input in spatial and time dimensions (Blakemore et al., 1970). Such an underlying pathophysiology could be located in the primary somatosensory cortex (Frasson et al., 2001, Inoue et al., 2004) and correspond to a defective or absent inhibitory neuronal population (Tamura et al., 2008).

Transferring this general pathophysiological model of defective somatosensory cortical inhibition on our results allows further specific interpretation for orofacial dystonia.

In the current study we detected the somatosensory cortex being underactive during a passive sensory stimulation, particularly of the clinically affected face.

It was shown that a diminished BOLD signal can be interpreted as a reduction of regional neuronal inhibition (Logothetis and Pfeuffer, 2004), or in other terms, express local disinhibition and increased cortical excitability.

Thus detected underactivity could be seen as an expression of an abnormal neuronal inhibition within the primary somatosensory face representation in orofacial dystonia.

Abnormal neuronal inhibition most likely leads to incorrect development of motor-programs, inappropriate sensory guidance of the motor cortex and could finally result in deficits in the control over motor execution with the characteristic motor- abnormalities present in dystonia (Frasson et al., 2001).

On the other hand somatosensory overactivity as previously seen in orofacial dystonia during motor execution (Dresel et al., 2006) could represent an attempt to reduce exceeding motor activity within the sensorimotor feedback loops, e.g. by an overactive somatosensory cortex modulating motor cortex activation.

It is thus conceivable to have dynamic somatosensory cortex responses with different activation patterns depending on the kind of experimental design, e.g. active motor vs. passive sensory stimulation tasks.

A further important contributor to the integration of sensory information for the development of motor programs is represented by the basal ganglia (Lacruz et al., 1991; Pastor et al., 2004).
In focal hand dystonia basal ganglia were reported to be overactive during an fMRI sensory discrimination task (Peller et al., 2006). Thus failure of surround inhibition within the basal ganglia- thalamic circuit was discussed to be responsible for altered sensorimotor activation patterns in dystonia.

Activation in the basal ganglia was seen consistently in our study's within group analysis. No difference in basal ganglia activation was seen in comparison of patients preBTX and controls. Interestingly between group comparison of patients preBTX and postBTX showed significant activation difference within the basal ganglia. This finding might indicate an ebbing excitability within the basal ganglia- thalamic circuits under botulinum toxin treatment.

The theory of an abnormal cortical plasticity in dystonia was demonstrated for the somatosensory system (Bara-Jimenez et al., 2000, Tinazzi et al., 2000) and used to explain disorders in motorcortex activity and plasticity (Hallett, 1995; Byl et al., 1996; Abbruzzese and Berardelli, 2003).
Further this theory connects to alterations in somatosensory cortex plasticity and topography (Hallett 2006) with changes in somatosensory representation in dystonia as reported for finger-representation during tactile stimulation in focal hand dystonia using somatosensory-evoked potentials (Bara-Jimenez et al., 1998) and fMRI (Butterworth et al., 2003).
Dedifferentiation and extension of cortical hand and finger representation due to increased cortical plasticity, as well as sensory receptive field enlargement and overlap was also shown in invasive electrophysiological mapping in animal models for occupation-induced focal hand dystonia (Byl et al., 1996).
Therefore acquired cortical misinterpretation of sensory input induced by skilled repetitive motor overuse was discussed to result in inappropriate motor output performance due to pathological adjustment of cortical organization. This mechanism was considered to

represent an important factor for the development of abnormal sensorimotor plasticity in man (Quartarone et al., 2006).
Due to close spatial proximity of cortical lip and forehead representation the differentiation between these areas was difficult in our study. Moreover this finding could be considered in the context of an increased plasticity with overlapping somatosensory cortex representations of the clinically affected face in patients.

Besides functional imaging studies, DTI and VBM studies focused likewise on abnormalities in patients with focal dystonia regarding the cortical and subcortical structures discussed above.
Analysis of gray matter by voxel- based morphometry (VBM) showed gray matter increase in patients with blepharospasm in bilateral globi pallidi (Egger et al., 2007) and the putamina (Etgen et al. 2006). Patients with blepharospasm had also bilateral gray matter increase in the caudate head, the cerebellum and decrease in the putamen and thalamus (Obermann et al., 2007).
Patients with focal hand dystonia showed increases (Garraux et al., 2004), but also decreases of gray matter in sensorimotor cortex, bilateral thalamus and cerebellum (Delmaire et al., 2007).
Another VBM study describes further abnormalities in sensorimotor areas with an increase in idiopathic cervical dystonia (Draganski et al., 2003).
All these results indicate subcortical gray matter changes to be a common finding in orofacial dystonia and other focal forms with a major contribution to the underlying pathophysiology (Obermann et al., 2007).

Further white matter analysis by diffusion tensor imaging (DTI) described specific subgyral alterations in sensorimotor out- and input pathways as well as supplementary motor areas and subcortical structures, such as basal ganglia and thalami with its surrounding white matter for various forms of dystonia (Carbon et al., 2004; Colosimo et al., 2005; Blood et al., 2006; Bonilha et al., 2007; Bonhila et al., 2009).
A recent study once again highlighted the importance of detected diffusion abnormalities in primary somatosensory cortex and their connections to subcortical structures in writer's

cramp (Delmaire et al., 2009) resembling an anatomical crosslink to these strongly discussed structures.
Another group postulated white matter abnormalities in cerebellothalamocortical pathways in genetic carriers to be capable of determining clinical manifestation of dystonia, based on detected fiber tract patterns (Argyelan et al., 2009).

Further additional functional mapping approaches such as single photon emission computed tomography (SPECT), using a gamma ray emitting tracer, is used to map neurotransmitter and to contribute to the understanding of receptor function in the pathogenesis of dystonia. With this approach it was possible to demonstrate postsynaptic dopaminergic dysfunction in the striatum in patients with cranial (Perlmutter et al., 1997), cervical (Hierholzer et al., 1994; Naumann et al., 1998) and focal hand dystonia (Horstink et al., 1997; Perlmutter et al., 1997).

Summarizing the different approaches in research, functional imaging approaches like fMRI, PET and SPECT highlight the significance of an abnormal somatosensory system in the motor disorder dystonia.
DTI and VBM approaches deliver information for the identification of disease associated pathological findings in gray and white matter.
Synopsis of anatomical and functional imaging results underline the importance of the somatosensory system amongst the main centers of pathological interest in focal dystonia: the somatosensory and motor cortex, the basal ganglia and their interaction.

4.4 Botulinum toxin and sensory training effects on the somatosensory cortex

No effect of botulinum toxin treatment was seen on somatosensory cortex response to tactile stimulation in patients with orofacial dystonia. However, we found a functional treatment correlate in subcortical structures, such as the basal ganglia and the thalami during stimulation of the forehead.

Botulinum toxin is a well-established and potent drug in the treatment of focal dystonia (Jankovic et al., 2004).

Despite of obvious clinical symptom improvement, it is not completely understood in which way the peripheral application has an influence on the primary central pathomechanism triggering dystonia and whether it modulates primary pathomechanisms at all.
In our study we recorded significant clinical improvement in four out of five rating scales, however, we detected no significant treatment effect on cortical information processing within the primary and secondary somatosensory cortex.
Absent treatment effects on primary and secondary somatosensory cortex abnormalities could therefore indicate primary contribution of the somatosensory cortex to the underlying pathology of orofacial dystonia.
In comparison to patients after treatment with botulinum toxin, untreated patients showed stronger contralateral basal ganglia and bilateral thalamus activations after stimulation of the forehead. This observation could not be made during stimulation of the upper lip.
Our studies data show that peripheral application of botulinum toxin seems to have an effect on subcortical activation patterns in orofacial dystonia induced by tactile stimulation within the dermatome supplied by the first, however not by the second, trigeminal division.
This finding is comprehensible, since the first trigeminal division was stimulated in an area in which periorbital botulinum toxin injections were applied, whereas the second trigeminal division was stimulated in an area more distant and closer to the upper lip than to the eye.
This finding might indicate an ebbing excitability in terms of a reduced disinhibition within the basal ganglia- thalamic circuits under botulinum toxin treatment and contribute to the beneficial effects of botulinum toxin application.

Further one previous functional imaging study detected an effect of botulinum toxin on the somatosensory cortex activation with a partial reduction of somatosensory overactivity in a subgroup of orofacial dystonia during a whistling task (Dresel et a., 2006). The authors observed a functional correlate under botulinum toxin treatment in patients with Meige's syndrome with a significant reduction of activation within the right postcentral gyrus and the adjacent right inferior parietal lobe as well as the left caudal mesial premotor areas.
Thus abnormal somatosensory cortex activation patterns seem to respond during motor performance of the dystonic limb, but not during our passive stimulation tasks.

On the one hand this may be due to a lacking or an undetectable effect of botulinum toxin on the processing of passive sensory information in general.
On the other hand this result may indicate the fundamental significance of the somatosensory system in the primary pathogenesis of orofacial dystonia in specific.

In an effort to understand the underlying mechanisms causing the detected botulinum toxin induced functional changes, results of other research approaches have to be taken into consideration.
In transcranial magnetic stimulation studies patients with upper limb dystonia showed differences in inhibitory cortical responses in comparison to controls and during the course of botulinum toxin treatment. One month after injection the initially lowered inhibitory responses adjusted to normal values of controls and returned to its abnormal starting point within two months. The authors suggested this finding to be based on the temporary reorganization of inhibitory circuits within the motor cortex (Gilio et al., 2000).
This central effect of botulinum toxin was attributed to either modulation of peripheral sensory input by denervation of peripheral nerves (Gilio et al., 2000, Hallett et al., 2000b), e.g. through alterations in afferent muscle spindle signals (Currà et al., 2004), or minimization of dystonic symptoms during the actual course of motion (Hallett, 2000a).

However, the application of botulinum toxin is not the only therapeutic approach in the treatment of focal dystonia. Other alternative or complementary therapeutic approaches, such as sensorimotor training, outline the importance of the sensorimotor system in focal dystonia.
Sensory training was discussed to have a positive effect on dystonic upper limb symptoms based on findings in animals and man.
Thus cortical somatosensory reorganization by sensory perception training was discussed to be possible based on the findings reported for an animal model (Byl et al., 1996).
In focal hand dystonia abnormal sensorimotor organization seemed to be modulated and even reorganized to a more sophisticated pattern by proprioceptive stimulation training offering a potential therapy approach in man (Rosenkranz et al., 2008).

Further clinical improvement was seen in patients with focal hand dystonia using Braille reading as sensory training. Patients experienced improvements in spatial discrimination and a decrease in disabilities (Zeuner et al., 2002). Mild symptom improvement in focal hand dystonia has also been reported for specific and unspecific motor training (Zeuner et al., 2008), but showed no regress in motor cortex abnormalities (Zeuner et al., 2005).

Symptoms were observed to return when training stopped, raising the question whether cortical plasticity can achieve a short time rebalance of sensory receptive fields without eliminating the actual pathophysiology in form of an abnormal inhibition (Hallett, 2009).

4.5 Somatotopy and cortical representation of stimulated areas

Besides the described somatosensory cortex abnormalities in orofacial dystonia, this study's data further allowed to confirm the somatotopic organization within the primary somatosensory cortex in healthy controls.

A distinction between hand and face representation was possible with the hand area being located medial, superior, and posterior to the face representation.

This finding is in line with findings reported from PET (Fox et al. 1987) or a multimodal imaging approach, using magnetoencephalography and fMRI, which allowed the distinction between a finger and lip representation area (Schulz et al., 2004). Other fMRI studies with stimuli applied by fully automated air puffs (Servos et al., 1999, Huang and Sereno 2007) or by the tactile stimulation device used in this study (Dresel et al. 2008) show similar somatotopic orientation.

This study showed close adjacency of lip and forehead representation. In patients a clear distinction between the lip and the forehead representation was difficult. The representation of the face was located close to the Sylvian fissure and the secondary somatosensory cortex. The findings in controls support the theory of an inverted face representation in primary somatosensory cortex with the lip representation in a superior and medial position to the forehead representation (Servos et al., 1999).

Other tactile fMRI stimulation experiments found an upright contralateral primary somatosensory cortex representation of the face (Iannetti et al. 2003, Huang and Sereno, 2007).

Bilateral secondary somatosensory cortex activation as seen in this study is in line with previous findings (Graham et al., 2001; Hagen and Pardo, 2002; Huang and Sereno, 2007; Dresel et al., 2008), also stronger secondary somatosensory cortex activation contralateral to the side of the stimulation was reported before (Hagen and Pardo, 2002).

Activations in secondary somatosensory cortex found in this study fit descriptions of other authors with secondary somatosensory cortex response to stimuli within the postcentral gyrus on the upper bank of the Sylvian fissure (Gelnar et al., 1998; Golaszewski et al., 2002; Iannetti et al., 2003, Huang and Sereno, 2007), posterior insula (Davis et al., 1998; Golaszewski et al., 2002, Dresel et al., 2008) and the inferior parietal lobule (Golaszewski et al., 2002; Hagen and Pardo, 2002) and were identified as Brodmann areas 5 (Francis et al., 2000), 40 and 43 (Iannetti et al., 2003).

4.6 Limitations of the study

FMRI offers a low risk, high resolution and non invasive approach using the BOLD effect as endogenous contrast agent to evaluate brain functions in vivo. Unlike PET and CT it is not based on ionizing radiation and measurements can therefore be repeated arbitrarily. With wide availability of MRI scanners fMRI enables an easy accessible and effective tool in the research on cortical network functions as demonstrated in this study for an abnormal somatosensory network in orofacial dystonia.

With ongoing progress in MRI technique fMRI encounters further optimization by the introduction of 3- Tesla MRI scanners regarding the signal to noise ratio and the sensitivity in the detection of neuronal activations and functional networks (Nakai et al., 2001).

But fMRI also encounters limitations.

Since fMRI detects a surrogate signal of the underlying neuronal activity, distinction between inhibitory and excitatory signals is difficult as well as determination whether a signal is based on local in- or output circuits (Logothetis, 2008).

Differentiation of the exact type of active neuronal cell clusters during a task is not possible and the spatial resolution is not high enough to identify neuronal populations. However complementary approaches such as invasive EEG mapping and histological approaches carry disproportionate risks and lack of acceptance in research on humans.

With superior spatial resolution, especially in subcortical structures in comparison to EEG and MEG, fMRI lacks of equal temporal resolution regarding the continuous recording in EEG. In fMRI the examiner receives an image, depending on the sequence, in an interval of one to four seconds only (Constable and Spencer 2001).

Besides EPI sequences are sensitive to susceptibility artefacts at tissue-bone or air interfaces, especially in frontobasal and temporobasal brain regions, leading to signal dropouts due to predisposed magnetic field inhomogeneities. Volume- selective z-shimming can increase the locally reduced BOLD sensitivity in these areas, especially at higher magnetic field strengths such as 3 Tesla (Weiskopf et al., 2006).

Further the hemodynamic response depends on the subjects compliance and may be modified by physiological processes, e.g. habituation, or individual subject confounders, e.g. lack of attention (Arthurs et al., 2004; Hämäläinen et al., 2000; Hoechstetter et al., 2000), motivation or anticipation (Carlsson et al., 2000; Porro et al., 2004).

Therefore event-related study designs were suggested to be used for the mapping of touch-induced somatosensory activation patterns due to increased sensitivity for primary somatosensory cortex responses (Dresel et al., 2008).

Besides subject and experimental specific factors, fMRI findings further depend on methodological factors such as data acquisition techniques and post-experimental statistical evaluation (Logothetis, 2008).

All these factors may complicate the comparison of fMRI results between various studies and have an impact on a study's validity and reproducibility.

In the future multimodal approaches could be performed in neuroscience studies allowing one method to compensate the shortcomings of the other. This could be done with already established combinations of e.g. non- invasive electrophysiological (EEG), which can directly assess the brain's electrical activity in real time but poor spatial resolution, and fMRI mapping (Logothetis, 2008), as well as novel combinations of imaging methods. This could for instance imply the combination of PET and fMRI with recently introduced hybrid PET-MRI scanners.

Thus analysis of hemodynamic responses with fMRI could be combined with simultaneous examination of glucose utilization or neurotransmitter release in specific structures, e.g. the basal ganglia, with PET. Such a method would not only allow new insights in pathologic

conditions of the brain, but also enable basic research on various cortical mechanisms in vivo.

5. Conclusion

Comparison of primary and secondary somatosensory activation patterns in fMRI during fully automated tactile stimulation of the forehead, upper lip and hands in patients with orofacial dystonia and controls allowed the identification of an abnormal cortical representation particularly of the clinically affected face in patients.

This finding was discussed in the context of an inaccurate cortical inhibition within the somatosensory cortex, ultimately leading to deficits in control over motor execution and characteristic motor- abnormalities in orofacial dystonia.

Abnormal cortical activation was also seen in patients during right sided stimulation of the clinically unaffected hand. This finding could indicate a general failure in the processing of sensory information in orofacial dystonia.

Using the same methods further research on somatosensory cortex responses in other forms of focal dystonia will be necessary to characterize general and maybe specific somatosensory abnormalities in cortical activation patterns for each dystonic condition.

Despite of significant clinical symptom improvement under treatment with botulinum toxin, no cortical effect could be identified in the primary or secondary somatosensory cortex.

This might be either due to the primary contribution of a defective somatosensory system with a lacking effect of botulinum toxin, or due to the methodological approach itself by application of strictly passive stimuli.

Instead we detected a treatment effect on subcortical activation patterns within the thalami and the contralateral putamen during stimulation of the first trigeminal division in patients before botulinum toxin injection compared to patients after treatment. No correlate was found during stimulation of the second trigeminal division, since stimulation of the second trigeminal division was closer to the upper lip than to the area of periorbital botulinum toxin injections.

Reduction of this abnormal subcortical activation pattern under botulinum toxin therapy may indicate an ebbing excitability within the basal ganglia- thalamic circuits and contribute to the beneficial effects of botulinum toxin therapy.

6. Abstract English

Background: The etiology and pathophysiology of idiopathic dystonia is yet incompletely understood. Neurophysiological and functional imaging studies previously indicated the importance of an abnormal somatosensory cortex in various forms of focal dystonia, including abnormal somatosensory cortex activations in the two types of orofacial dystonia examined in this study, Blepharospasm and Meige's syndrome.

Methods: We used functional magnetic resonance imaging (fMRI) to map and compare somatosensory cortex responses to tactile stimuli applied to the forehead, upper lip and hands by a recently introduced fully automated stimulation device (Dresel et al., 2008). This study aims to explore abnormalities within the somatosensory system in 16 patients with orofacial dystonia in comparison to 15 healthy controls.

In the course of botulinum toxin treatment patients were scanned twice in order to detect a possible treatment effect on somatosensory activation patterns.

Results: Tactile stimulation of the clinically affected face, but also of the unaffected right hand, yielded abnormal primary and secondary somatosensory cortex activations in orofacial dystonia. Cortical somatosensory activation patterns did not change under treatment with botulinum toxin, however, a functional correlate of treatment was detected in the basal ganglia and the thalami.

Conclusion: Abnormalities within the somatosensory representation indicate the importance of an abnormal somatosensory system in the underlying pathophysiology of orofacial dystonia and were discussed in the context of increased cortical plasticity and defective surround inhibition. Botulinum toxin seemed to have an effect on subcortical sensory processing.

7. Abstract German

Hintergrund: Die zu Grunde liegende Ätiologie der idiopathischen Dystonien, insbesondere auch der in dieser funktionellen Kernspinstudie (fMRT) untersuchten Unterformen der orofazialen Dystonien Blepharospasmus und Meige-Syndrom, ist noch nicht verstanden. Neurophysiologische und fMRT Studien deuten jedoch vermehrt auf die Rolle eines fehlerhaften somatosensorischen Systems hin.

Methoden: Um Unterschiede in der somatosensorischen Verarbeitung auf taktile Stimulationen bei Patienten mit orofazialer Dystonie und gesunden Kontrollpersonen zu charakterisieren, benutzten wir eine voll automatisierte Stimulationsanlage (Dresel et al., 2008) mit der die Stirn, Oberlippe und Hände der Patienten stimuliert wurden. Hierfür untersuchten wir 16 Patienten mit orofazialer Dystonie, davon 12 mit Meige-Syndrom und 4 mit Blepharospasmus, sowie 15 gesunde Probanden. Um einen möglichen Effekt der Behandlung mit Botulinumtoxin auf somatosensorische Aktivierungsmuster aufzuzeigen, wurden die Patienten während eines Behandlungszykluses vor und nach Injektionen von Botulinumtoxin untersucht.

Ergebnisse: Patienten mit orofazialer Dystonie zeigten eine von den Kontrollpersonen veränderte primär und sekundär somatosensorische Repräsentation der klinisch betroffenen Gesichtsregion, aber auch der nicht betroffenen rechten Hand. Die kortikalen somatosensorischen Aktivierungsmuster wurden nicht von der Behandlung mit Botulinumtoxin moduliert. Jedoch fand sich ein Unterschied in subkortikalen Strukturen, wie den Basalganglien und den Thalami.

Zusammenfassung: Zu gesunden Probanden veränderte somatosensorische Antworten auf taktile Stimulationen zeigen den Einfluss eines abnormen somatosensorischen Systems in der zu Grunde liegenden Pathophysiologie der orofazialen Dystonien. Sie werden unter den Gesichtspunkten der gängigen pathophysiologischen Modelle für die fokalen Dystonien hinsichtlich einer veränderten kortikalen Plastizität sowie einer gestörten neuronalen Inhibition diskutiert.

Die Behandlung mit Botulinumtoxin scheint Einfluss auf die subkorticale sensorische Informationsverarbeitung zu haben.

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