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Altered Sensorimotor Activation Patterns in Idiopathic Dystonia—An Activation Likelihood Estimation Meta-Analysis of Functional Brain Imaging Studies

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Abstract: Dystonia is characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements or postures. Functional neuroimaging studies have yielded abnormal task-related sensorimotor activation in dystonia, but the results appear to be rather variable across studies. Further, study size was usually small including different types of dystonia. Here we performed an activation likelihood estimation (ALE) meta-analysis of functional neuroimaging studies in patients with primary dystonia to test for convergence of dystonia-related alterations in task-related activity across studies. Activation likelihood estimates were based on previously reported regional maxima of task-related increases or decreases in dystonia patients compared to healthy controls. The meta-analyses encompassed data from 179 patients with dystonia reported in 18 functional neuroimaging studies using a range of sensorimotor tasks. Patients with dystonia showed bilateral increases in task-related activation in the parietal operculum and ventral postcentral gyrus as well as right middle temporal gyrus. Decreases in task-related activation converged in left supplementary motor area and left postcentral gyrus, right superior temporal gyrus and dorsal midbrain. Apart from the midbrain cluster, all between-group differences in task-related activity were retrieved in a sub-analysis including only the 14 studies on patients with focal dystonia. For focal dystonia, an additional cluster of increased sensorimotor activation emerged in the caudal cingulate motor zone. The results show that dystonia is consistently associated with abnormal somatosensory processing in

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the primary and secondary somatosensory cortex along with abnormal sensorimotor activation of mesial premotor and right lateral temporal cortex. *Hum Brain Mapp 37:547–557, 2016.*

Key words: primary dystonia; functional magnetic resonance imaging; positron emission tomography; meta analyses; sensorimotor

INTRODUCTION

Dystonia is a movement disorder characterized by "sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both" [Albanese et al., 2013]. Primary dystonia has many faces presenting a wide spectrum of clinical manifestations ranging from focal dystonia affecting a group of muscles in a single body part, to generalized dystonia involving the whole body. Dystonia may be continuously present, manifest itself intermittently, or be restricted to a specific task [Phukan et al., 2011]. The pathophysiology underlying dystonia still remains unclear [Neychev et al., 2011]. An increasing number of molecular causes have been revealed, but a shared genetic etiology may result in a wide spectrum of clinical manifestations. For instance, the genetic form of primary torsion dystonia, called DYT1 dystonia may present as severe generalized dystonia, but also as focal or segmental dystonia [Bressman et al., 1989]. Despite of the variety of causes and clinical presentations of dystonia, shared clinical features suggest common mechanisms of pathogenesis. In terms of pathophysiology, deficient inhibition, sensory dysfunction, and aberrant sensorimotor plasticity are key abnormalities, which are shared by different clinical phenotypes [Defazio et al., 2007; Quartarone et al., 2006; Sohn and Hallett 2004].

Functional neuroimaging has been used in a series of studies to identify alterations in task-related activation of the sensorimotor network, mainly in patients with focal forms of primary dystonia. These studies have yielded abnormal activation patterns in the sensorimotor network, but findings have been heterogeneous. This may be attributed to the fact that the task employed to map sensorimotor activation varied across studies. Most studies included only a relatively small number of patients and focused on different types of dystonia. Therefore, it remains unclear whether primary dystonia is associated with task-related alterations in sensorimotor networks that are consistent across tasks and sub-types of dystonia.

To address this question, we applied activation likelihood estimation (ALE) meta-analyses of published functional neuroimaging studies in patients with primary dystonia [Eickhoff et al., 2012]. This approach allowed us to test for convergence of disease-related alterations in neural activity reported in previous studies. We deliberately chose to investigate changes associated with primary dystonia irrespective of the subtypes (i.e., focal, generalized etc.) or the type of sensorimotor task, because we aimed to identify general mechanisms and common pathways involved in the pathophysiology of primary dystonia.

Abbreviations

ALE	Activation likelihood estimation
FEW	Family-wise error
MA	Modeled activation
PET	Positron emission tomography
SMA	Supplementary motor area
VCA	Vertical commissure anterior

METHODS

Literature Search and Study Selection

We conducted a literature search on Pubmed (www.pubmed.org) with the strings: "Dystonia" OR "spasmodic dysphonia" OR "blepharospasm" OR "writer* cramp" OR "Meige" AND "fMRI" OR "functional MRI" OR "functional magnetic resonance" OR "PET" OR "positron emission tomography" resulting in 256 results on August 1, 2013. Additionally, we searched review papers and references of retrieved articles for further studies.

We included all fMRI or [^{15}O]H2O positron emission tomography (PET) studies on patients with primary dystonia, which (i) compared activation patterns in dystonic patients to a matched healthy control group, (ii) applied motor, sensory or motor imagery tasks and (iii) were published in English. These studies were screened for eligibility and excluded if they (i) were review articles reporting no original data, (ii) did not compare dystonia patients and healthy controls in a whole-brain analysis (i.e., region of interest analyses, multivariate analyses or covariate analyses), (iii) included less than five patients, (iv) tested different tasks against each other rather than against baseline. We contacted the authors if stereotactic coordinates of maxima of the between-group comparison were not provided in the article. This resulted in 18 studies that were included in the meta-analyses (Table I): [Ali et al., 2006; Carbon et al., 2010; Ceballos-Baumann et al., 1995, 1997; de Vries et al., 2008; Dresel et al., 2006; Havrankova et al., 2012; Ibanez et al., 1999; Kadota et al., 2010; Lerner et al. 2004; Obermann et al., 2010; Opavsky et al., 2011, 2012; Peller et al., 2006; Playford et al., 1998; Preibisch et al., 2001; Schrag et al., 2013; Simonyan and Ludlow, 2010].

Activation Likelihood Estimation (ALE)

For the meta-analyses, the revised version [Eickhoff et al., 2012] of the ALE approach for coordinate-based

TABLE I. Studies included in the meta-analysis

Study		Modality	# Dys	# C	Handed-ness	Age Dys	Age C	# Foci	Contrast
De Vries et al., 2008		fMRI	8	9	Right	30–55	31–52		
Cervical dystonia	**Task**:	Imagery: Extension flexion of right hand						12	Dys<C
		Motor: Extension flexion of right hand						4	Dys<C
		Motor: Clenching of right hand						1	Dys<C
Dresel et al., 2006		fMRI	13	13	Right	62.4	54.8		
Meige	**Task**:	Whistling						3	Dys>C
								4	Dys<C
Blepharospasm	**Task**:	Whistling						6	Dys>C
								2	Dys<C
Havrankova et al., 2012		fMRI	11	11	Right	41.5	44.6		
Writers Cramp	**Task**:	Writing and random drawing with right hand						9	Dys<C
Kadota et al., 2010		fMRI	7	10	Right	28.6	28.5		
Musicians Dystonia	**Task**:	Tapping with right hand						1	Dys>C
		Tapping with both hands						1	Dys<C
Opavsky et al., 2011		fMRI	7	9	Right	53.1	55.2		
Cervical dystonia	**Task**:	Ipsilateral finger opposition test						1	Dys>C
Preibisch et al., 2001		fMRI	12	10	Right	43.5	34.1		
Writers cramp	**Task**:	Writing with right hand						1	Dys>C
								4	Dys<C
Obermann et al., 2010		fMRI	17	17	Right	61.2	59.6		
Cervical dystonia	**Task**:	Passive flexion of left forearm						6	Dys>C
Opavsky et al., 2012		fMRI	7	9	Right	53.1	55.2		
Cervical dystonia	**Task**:	Electrical stimulation of median nerve ipsilateral to head turning						2	Dys<C
Simonyan and Ludlow, 2010		fMRI	11	11	Right	50.6	55.7		
ADSD	**Task**:	Symptomatic voice production						14	Dys>C
								1	Dys<C
		Asymptomatic coughing						7	Dys>C
								1	Dys<C
		Asymptomatic breathing						2	Dys>C
								8	Dys<C
		Asymptomatic whimper						8	Dys>C
								6	Dys<C
		fMRI	11	11	Right	56.6	55.7		
ABSD	**Task**:	Symptomatic voice production						12	Dys>C
								2	Dys<C
		Asymptomatic coughing						5	Dys>C
								7	Dys<C
		Asymptomatic breathing						4	Dys>C
								3	Dys<C
		Asymptomatic whimper						4	Dys>C
								3	Dys<C

TABLE I. (continued).

Study		Modality	# Dys	# C	Handed-ness	Age Dys	Age C	# Foci	Contrast
Peller et al., 2006		fMRI	17	17	Right	50.6	49.8		
Writers cramp	**Task**:	Sensory discrimination task (orientation of gratings) with right index finger						23	Dys>C
Schrag et al., 2013		PET	5	6	–	35.2	31		
ITD	**Task**:	Flexion of right foot						14	Dys>C
								6	Dys<C
Carbon et al. 2010		PET	9	12	Right	46.1	44.7		
ITD	**Task**:	Motor: reaching counter-clock-wise with right hand.						2	Dys>C
Lerner et al., 2004		PET	10	10	Right	–	–		
Writers cramp	**Task**:	Tapping with right hand						1	Dys>C
								1	Dys<C
	Task:	Writing with right hand						2	Dys>C
								1	Dys<C
Ibanez et al. 1999		PET	7	7	Right	42	39		
Writers cramp	**Task**:	Sustained contraction of right hand						1	Dys<C
	Task:	Writing with right hand						3	Dys<C
Playford et al., 1998		PET	6	6	–	33	32		
ITD	**Task**:	Free selection of joystick movement with right hand						8	Dys>C
Ceballos-Baumann et al., 1997		PET	6	6	Right	53	47		
Writers cramp	**Task**:	Writing task with right hand						6	Dys>C
								6	Dys<C
Ceballos-Baumann et al., 1995		PET	6	6	–	33.3	39		
ITD	**Task**:	Free selection of joystick movement with right hand						11	Dys>C
								5	Dys<C
Ali et al., 2006		PET	9	10	Right	46	35		
Spasmodic dysphonia	**Task**:	Narrative speech						9	Dys>C
								7	Dys<C
	Task:	Narrative whispering						4	Dys<C

Dys # C, number of patients with dystonia and controls enrolled in the respective study; # Foci, number of activation foci reported in the respective study. ITD: idiopathic torsion dystonia, ADSD: adductor spasmodic dysphonia, ABSD: abductor spasmodic dysphonia

meta-analyses was used [Turkeltaub et al., 2002]. ALE has been described in detail previously [Eickhoff et al., 2009, 2012; Turkeltaub et al., 2012]. ALE was applied to assess convergence of activation maxima, which were reported to be increased or decreased in dystonia patients compared to healthy controls in the different experiments. The term "experiment" refers to a contrast, e.g., "Dystonia during task A > Control during task A" in a given study. Thus, one study can comprise several experiments.

The reported maxima for activation differences between dystonia patients and healthy controls were modeled as three-dimensional Gaussian probability distributions. The size of these distributions depended on the number of patients enrolled in the respective experiment to take into account sample-size related uncertainty about the exact localization of the maxima. For each experiment a modeled activation (MA) map was computed, which contained the combined probability for activation differences between dystonia patients and healthy controls based on the reported maxima. By taking the union of all MA maps (i.e., from all experiments), ALE scores were computed at each grey matter voxel describing the convergence of results across all experiments. The significance of convergence of reported activation maxima were compared to a random distribution of activation foci. Results were thresholded at $P < 0.05$ family-wise error (FWE) corrected at the cluster-level.

In addition to the main meta-analyses described above, we performed separate post hoc meta-analyses which only included manual motor tasks or tasks engaging face and laryngeal muscles.

Finally, to assess abnormal neural activity related to the distribution of dystonia, i.e., generalized vs. not-generalized dystonia, we conducted additional meta-analyses only including studies, which tested patients with focal forms of dystonia ($n = 14$). Note that there were not enough studies to conduct a separate analysis for generalized dystonia ($n = 4$).

Anatomical assignment of the resulting activation clusters was achieved using the SPM Anatomy toolbox, which relies on previous studies that provided details about cytoarchitecture and intersubject variability of brain areas [Eickhoff et al., 2007b] for localization of significant effects.

RESULTS

We included 10 fMRI and 8 [15O]H2O PET studies in the ALE meta-analyses. These studies had an average sample-size of 9.3 ± 3.6 (mean $\pm$ SD) dystonia patients and 9.9 ± 3.3 control participants (Table I) and reported results from 18 experiments and 101 patients for the contrast "Dystonia > Controls" as well as 21 experiments and 105 patients for the contrasts "Dystonia < Controls". Many neuroimaging studies investigated patients with writer's cramp or other forms of focal hand dystonia, but also other forms of focal or segmental dystonia (torticollis, blepharospasms, oromandibular dystonia, and laryngeal dystonia) as well as generalized dystonia had been studied (Table I). Studies of paroxystic dystonia or dystonic tremor were not found using our search profile.

The ALE meta-analysis showed consistent increases in task-related activation in patients with dystonia relative to healthy controls. Significant convergence of activation maxima was found in the somatosensory cortex as well as the right middle temporal gyrus (Table II, Fig. 1). In the somatosensory cortex, increased activation was found almost mirrored symmetrically in both hemispheres with two distinct activation maxima in each hemisphere. One maximum was located in the rostral part of the parietal operculum and belonged to the secondary somatosensory cortex (S2), while the other maximum was located in the ventral part of the primary somatosensory area (S1), which contains the sensory presentations of the larynx and face.

The ALE meta-analysis also yielded consistent decreases in task-related activation in dystonia patients relative to healthy controls. ALE showed convergence of activation maxima in the supplementary motor area (SMA), left postcentral gyrus, right superior temporal gyrus and dorsal midbrain, extending into the thalamus and cerebellum (Table II, Fig. 1). The deactivation maxima in SMA were located in the transition zone between SMA-proper and rostral SMA, extending into the very dorsal part of the anterior cingulate cortex. The maximum in the postcentral gyrus showing decreased task-related activation in dystonic patients was located within the hand representation of S1 which was more dorsally than the maximum showing increased task-related activation (Fig. 1).

We also conducted meta-analyses separately for tasks probing face or laryngeal muscles and tasks engaging hand muscles. The analysis only considering movements of face/laryngeal muscles showed the same bilateral increase in the sensory face area in patients with dystonia as the main meta-analyses. However, the motor-related decrease in the hand area of dystonia patients was not present. Conversely, only considering manual motor tasks yielded a consistent increase in the postcentral gyrus in the hand area of dystonia patients (Fig. 2), which was not present in the main meta-analyses, while the increase in the sensory face area disappeared.

Finally, ALE based on the 14 studies on patients with focal and segmental dystonia revealed an increase in task-related activation in the left caudal cingulate gyrus (Fig. 3). This activation maximum did not emerge in the meta-analysis including all forms of primary dystonia and was located ventrally to the SMA cluster where dystonic patients showed a decrease in task-related activation. Further, the activity decrease in the dorsal midbrain was no longer significant, when ALE was restricted to the 14 studies on focal dystonia. All other between-group differences in task-related sensorimotor activations that were found in the meta-analyses including all forms of primary dystonia, remained significant in the meta-analyses including only patients with focal and segmental dystonia.

TABLE II. Activation-likelihood-estimation analyses for between-group contrasts

Neural region	Side	MNI coordinates (mm) X	Y	Z	z-value
Increased activation between dystonia and controls (18 experiments, 101 patients)					
Cluster 1:					
Maximum 1: pre-central gyrus, M1	Right	50	−4	30	7.47
Maximum 2: Inferior parietal lobule, S2	Right	60	−14	10	5.72
Cluster 2:					
Maximum 1: Primary somatosensory cortex, S1	Left	−54	−2	20	6.38
Cluster 3:					
Maximum 1: Primary somatosensory cortex, S1	Left	−38	−16	36	5.56
Maximum 2: Inferior parietal lobule, S2	Left	−48	−8	34	5.20
Cluster 4:					
Maximum 1: Middle temporal gyrus	Right	60	−30	−4	5.36
Decreased activation between dystonia and controls (21 experiments, 105 patients)					
Cluster 1:					
Maximum 1: preSMA/SMA	Left	−8	0	54	5.48
Maximum 2: preSMA/ACC	Left	−2	12	48	4.58
Maximum 3: SMA	Left	−16	−8	62	3.24
Cluster 2:					
Maximum 1: dorsal midbrain[a]		2	−30	−6	4.29
Maximum 2: left cerebellum	Left	−8	−36	−12	3.45
Maximum 3: right thalamus	Right	4	−18	2	3.29
Maximum 4: upper cerebellar vermis	Right	6	−36	−14	3.26
Cluster 3:					
Maximum 1: Superior temporal gyrus (middle part)	Right	50	−6	−8	4.09
Cluster 4:					
Maximum 1: Primary somatosensory cortex, S1[b]	Left	−52	−18	46	5.19

Clusters with convergence of activation maxima are reported at a statistical threshold of $P < 0.05$ cluster-corrected. Separate meta-analyses were performed where studies were divided into (i) experiments with hand vs face tasks and (ii) experiments with patients with focal and segmental vs all forms of dystonia.

[a]This cluster disappeared when only patients with focal and segmental dystonia were included. In addition, this meta-analysis showed increased activation of the middle cingulate gyrus (−4/12/38, z-value: 5.79) in patients with focal and segmental dystonia (see Fig. 3).

[b]This cluster did not remain significant when only considering face tasks. Only considering hand tasks showed increased activation of the left postcentral gyrus at the hand area (−40/-26/52, z-value: 4.71) in the contrast dystonia > control (see Fig. 2).

DISCUSSION

ALE meta-analyses identified regional changes in task-related activity in primary dystonia, which clustered in three cortical regions, including the somatosensory cortex, mesial pre-motor cortex, and right lateral temporal cortex. The most prominent differences in sensorimotor activation between patients and controls emerged in the anterior and inferior part of the parietal cortex. Patients showed a bilateral pattern of increased activation in S1 and S2 with two distinct activation maxima in the ventral part of the postcentral gyrus and the anterior part of the parietal operculum.

Primary Somatosensory Cortex (S1)

The postcentral region showing increased task-related activation in dystonia was located in the ventral region of S1 where the face and larynx are somatotopically represented. Conversely, a more dorsal cluster in the left postcentral gyrus, located within the hand representation of S1, showed the opposite pattern, namely a relative decrease in task-related activation in patients with dystonia.

We wondered whether the bilateral increase in task-related activation confined to the face area in S1 and the left-hemispheric reduction in activation confined to the S1 hand area were related to the differences in tasks used in experiments. This prompted us to conduct additional meta-analyses which only considered face-related experiments. This analysis showed increased activation of the sensory face area in dystonia patients, while the decrease in activation within the sensory hand area disappeared. Likewise, a meta-analysis which only included experiments involving manual motor tasks showed increased activation of the hand area in the postcentral gyrus, but no alterations in the face area. These patterns indicate that the location of altered activation in S1 has a somatotopic relation to the sensory feedback that is produced in the body part engaged in the task. The fact that most fMRI studies required patients to move the upper limb or oropharyngeal and laryngeal muscles may explain the lack of an

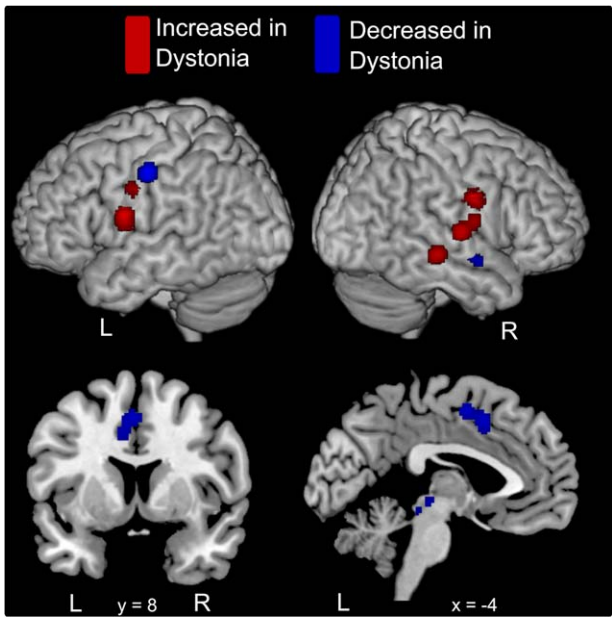

Figure 1.

Convergence of activation maxima for the group comparison between patients with dystonia and healthy controls. Red clusters indicate increased activity in dystonia patients compared to healthy controls, blue clusters indicate decreased activity in dystonia patients compared to healthy controls. Results are thresholded at $P < 0.05$ FWE corrected at the cluster level. L, left; R, right.

abnormal activity pattern in the leg representation of S1. This negative finding should therefore not be taken as evidence that sensory processing in the leg area is normal in dystonia.

The abnormal activation of S1 during sensorimotor tasks is in good agreement with a large body of research showing abnormal processing of somatosensory inputs in dystonia. First, sensory processing is impaired in dystonia, including temporal and spatial discrimination [Bara-Jimenez et al., 2000; Molloy et al 2003]. Second, aberrant cortical sensory processing and deficient afferent cortical inhibition has been demonstrated in patients with focal dystonia [Abbruzzese et al., 2001; Elbert et al., 1998]. Third, in a monkey model of task-specific hand dystonia, the emergence of dystonic symptoms was paralleled by a distortion and enlargement of sensory representations indicating aberrant sensory plasticity [Byl et al., 1996, Bara-Jimenez, 1998].

Secondary Somatosensory Cortex (S2)

Our meta-analysis also yielded an abnormal activation pattern in the S2. Relative to healthy controls, patients with dystonia showed a symmetrical over-activation in the parietal operculum. Eickhoff et al [2006] used an observer-independent approach to define areal borders, in the parietal opercular cortex. Based on differences in the cytoarchitectonic profile, observer-independent parcellation showed that the human parietal operculum consists of four subregions: areas OP 1-4. Areas =OP1, OP 4, and OP 3, thought to be human homologues of areas SII, PV, and VS, respectively [Eickhoff et al.,, 2006, Eickhoff et al., 2007a]. A somatotopic arrangement in SII was found in non-human primates and humans [Disbrow et al., 2000], and somatotopy distinguishing face, hand and trunk was confirmed

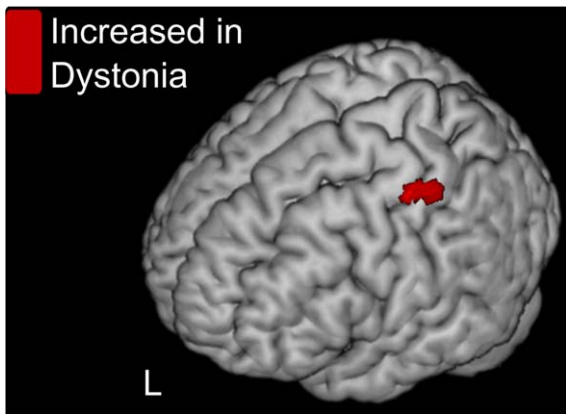

Figure 2.

When only considering studies with manual motor tasks, there was a consistent increase in the hand area of the left postcentral gyrus in patients with dystonia. Results are thresholded at $P < 0.05$ family-wise error corrected at the cluster level. L, left.

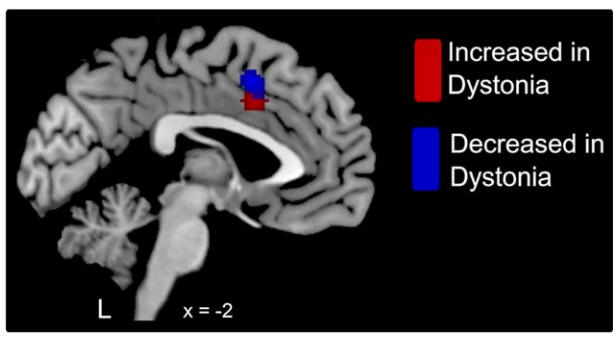

Figure 3.

Differences in activation between dystonia patients and healthy controls as revealed by meta-analyses discarding studies of patients with generalized dystonia. The figure illustrates the additional finding of increased middle cingulate gyrus activation in patients with focal and segmental dystonia compared to healthy controls (marked in red). Please note that all areas shown in Fig. 1 except the midbrain region also significantly differed between dystonia patients and healthy controls when discarding patients with generalized dystonia. Results are thresholded at $P < 0.05$ family-wise error corrected at the cluster level. L, left; R, right.

[Eickhoff et al., 2008]. The anatomical connectivity pattern suggests that the sub-regions SII (OP 1) and PV (OP 4) are implicated in integrating multimodal information across body parts [Disbrow et al., 2000]. Accordingly, the lateral parietal operculum was found to be activated in healthy subjects when they were touched and when they observed touching [Keysers et al., 2004]. Therefore, we hypothesize that the symmetric increase in the rostral part of the parietal operculum (area OP4) might reflect increased sensitivity to multimodal somatosensory input and deficient multisensory integration.

Mesial Premotor Areas

The meta-analysis detected impaired activation of the SMA in patients with dystonia. The SMA cluster was centered on the vertical commissure anterior (VCA) line (y = 0), which marks the transition zone from SMA-proper to pre-SMA. Since the SMA cluster extended into both, the rostral part of SMA-proper and the caudal part of pre-SMA, the ALE meta-analysis indicated deficient sensorimotor activation of both regions. The SMA-proper and pre-SMA are two functionally and structurally distinct areas. Therefore, we discuss the potential significance of the activity decrease in dystonia in these two areas separately.

The SMA-proper is closely interconnected with M1 and the motor part of the basal ganglia, and has direct connections to the spinal cord [Alexander et al., 1986; He et al., 1995; Muakkassa and Strick, 1979]. SMA-proper is activated during a variety of motor tasks, e.g., finger tapping [Boecker et al., 1994], sequential movements [Gerloff et al., 1997] or simple stimulus response paradigms [Kloppel et al., 2007] and is thought to be involved in core aspects of motor control such as motor preparation, -initiation, and -execution. The prominent role of SMA-proper in movement execution is reflected by its rostro-caudal somatotopical organization. The face and hand representations are located more rostrally and ventrally than the foot representations although there is substantial spatial overlap [Cauda et al., 2011; Chainay et al., 2004; Luppino et al., 1991]. Therefore, deficient task-related activation in rostral SMA-proper may be due to the fact that most neuroimaging studies in dystonia used tasks requiring manual or orofacial movements.

In contrast to SMA-proper, the pre-SMA is a prefrontal area subserving more cognitive aspects of motor control [Nachev et al., 2008], such as detecting and inhibiting erroneous responses [Mostofsky and Simmonds, 2008], switching between competing motor programs [Isoda and Hikosaka, 2007] and modulating the speed-accuracy tradeoff [Forstmann et al., 2008]. Our ALE meta-analysis revealed that the alterations in task-related activity also included the pre-SMA. This result shows that abnormal motor control extends beyond alterations in executive sensorimotor functions affecting cognitive aspects of motor control.

A sub-analysis of neuroimaging studies on patients with non-generalized dystonia revealed a cluster with increased activity in the mid-cingulate cortex, corresponding to the caudal cingulate motor zone [Picard and Strick, 2001]. The anterior cingulate zone has projections to premotor, primary motor and parietal areas, brainstem motor nuclei and spinal cord, which has been shown in monkey studies [Morecraft and Van Hoesen, 1992] and human tractography studies [Beckmann et al., 2009]. The caudal cingulate motor zone is an executive motor area, which contributes to context-sensitive control of actions for instance actions in response to pain [Perini et al., 2013]. Of note, an altered activation of the anterior cingulate area has been found in patients with focal musician's dystonia and was ascribed to abnormal error prediction and deficient feed forward control of motor commands [Lee et al., 2013].

Middle and Superior Temporal Gyrus

The meta-analysis revealed increased activation of the right posterior middle temporal gyrus (MTG) and decreased activation of the superior temporal gyrus (STG) in idiopathic dystonia. These regions are associated with language processing, and the studies that revealed these changes were primarily studies of spasmodic dysphonia with a vocalization or whispering task. It was previously described that the right STG was activated during voice processing [Belin et al., 2000], and exhibited stronger responses to a variety of vocally expressed emotions rather than to neutral prosody [Ethofer et al., 2009], with activation related to pitch [Peck et al., 2009]. The STG is reportedly involved in audio-motor integration for vocal production [Hickok et al., 2003] as well as conscious self-monitoring of speech output [Hashimoto and Sakai, 2003; Schulz et al., 2005]. Therefore, it is possible that the abnormal activations in the lateral temporal cortex might be related to abnormal self-monitoring of vocal output in dystonia.

Subcortical Structures

Our meta-analysis revealed decreased activation in the midbrain. Previously it was found that lesions in pontomesencephalic areas may elicit secondary dystonia [Loher and Krauss, 2009] and brain stem pathology has been described in DYT 1 dystonia [McNaught et al., 2004]. It was recently suggested that cervical dystonia is a disorder of a midbrain network for covert attentional orienting involving both the sensory and motor laminae of the superior colliculus [Hutchinson et al., 2014], and the result from the meta-analysis might fit with that theory.

The meta-analysis did not reveal consistent activity changes in the basal ganglia. However, this negative finding does not imply that the basal ganglia are not involved in the pathophysiology underlying dystonia. For instance, the putamen contralateral to the affected hand displayed a distorted somatotopic organization in patients with task-

specific hand dystonia [Delmaire et al., 2005]. Since an alteration of somatotopy might not translate into a significant change in task-related activation, such abnormalities might not be detected in a meta-analysis, which is based on magnitude differences in task-related activation between dystonic patients and healthy controls. Recent advances in fMRI using higher field strength might allow for a more fine-grained analysis of movement-related activation in the basal ganglia.

A growing body of evidence implicates cerebellar dysfunction in the pathophysiology of primary dystonia [for review, see Prudente et al., 2014]. We found a decreased activation in the left cerebellum and right cerebellar vermis that may corroborate the recent description of dystonia as a network disorder, involving both the cortico-striato-pallido-thalamo-cortical and cerebellothalamo-cortical pathways [Lehericy et al., 2013].

LIMITATIONS

This ALE study comprises a relatively low number of studies. 10 fMRI and 8 [^{15}O]H_2O PET studies. In addition, some of the experiments were conducted in the same patient group and thus do not constitute independent observations. Currently, no procedure exists to formally estimate a sufficient sample size in terms of studies, experiments, and subjects. A more conservative ALE in which only one MA map is generated for each subject group instead of each experiment [Turkeltaub et al., 2012] would significantly reduce power in the ALE analyses, which is already affected by the low number of studies that could be included. Furthermore, this approach would not take into account that different experimental tasks probe activity related to different aspects of sensorimotor control in dystonia.

CONCLUSIONS

Our meta-analytical approach identified several brain regions where patients with idiopathic dystonia displayed a consistent alteration in task-related activity during sensorimotor tasks. Activation changes converged on clusters in somatosensory areas, mesial premotor areas and superior and medial temporal gyrus. These regional changes in sensorimotor activity suggest that various forms of idiopathic dystonias share common abnormalities in sensorimotor integration that are consistently expressed across a range of motor tasks.

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