RESEARCH ARTICLE

Task-Specificity in Focal Dystonia Is Shaped by Aberrant Diversity of a Functional Network Kernel

Stefan Fuertinger, PhD[1] and Kristina Simonyan, MD, PhD[2,3]*

[1]Ernst Strüngmann Institute for Neuroscience in Cooperation with Max Planck Society, Frankfurt am Main, Germany
[2]Department of Otolaryngology, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, Massachusetts, USA
[3]Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

ABSTRACT: **Objectives**: Task-specific focal dystonia selectively affects the motor control during skilled and highly learned behaviors. Recent data suggest the role of neural network abnormalities in the development of the pathophysiological dystonic cascade.
Methods: We used resting-state functional MRI and analytic techniques rooted in network science and graph theory to examine the formation of abnormal subnetwork of highly influential brain regions, the functional network kernel, and its influence on aberrant dystonic connectivity specific to affected body region and skilled motor behavior.
Results: We found abnormal embedding of sensorimotor cortex and prefrontal thalamus in dystonic network kernel as a hallmark of task-specific focal dystonia. Dependent on the affected body region, aberrant functional specialization of the network kernel included regions of motor control management in focal hand dystonia (writer's cramp, musician's focal hand dystonia) and sensorimotor processing in laryngeal dystonia (spasmodic dysphonia, singer's laryngeal dystonia). Dependent on skilled motor behavior, the network kernel featured altered connectivity between sensory and motor execution circuits in musician's dystonia (musician's focal hand dystonia, singer's laryngeal dystonia) and abnormal integration of sensory feedback into motor planning and executive circuits in non-musician's dystonia (writer's cramp, spasmodic dysphonia).
Conclusions: Our study identified specific traits in disorganization of large-scale neural connectivity that underlie the common pathophysiology of task-specific focal dystonia while reflecting distinct symptomatology of its different forms. Identification of specialized regions of information transfer that influence dystonic network activity is an important step for future delineation of targets for neuromodulation as a potential therapeutic option of task-specific focal dystonia. © 2018 International Parkinson and Movement Disorder Society

Key Words: functional connectome; graph theory; network kernel; task-specific focal dystonia

Task-specific focal dystonia (TSFD) is characterized by selective activation of involuntary movements during precise and highly skilled behaviors, such as writing, playing a musical instrument, speaking, or singing. TSFD develops spontaneously in midlife and progresses into a chronic debilitating disorder, which causes emotional stress, social embarrassment, and oftentimes derails professional careers as in the case of musician's dystonia. By an estimate, TSFD has a prevalence of 15.4 per 100,000,[1] with as many as 2% of professional musicians developing dystonia.[2]

Although task specificity in dystonia is a clinically well-described phenomenon, its multifactorial pathophysiology is unknown. Several lines of evidence suggest that dystonia can be viewed as a functional network disorder with common abnormalities in basal ganglia, thalamus, cerebellum, and sensorimotor cortex.[3–7] On the other hand, it appears that different forms of dystonia, especially among TSFD, follow divergent pathophysiological mechanisms precipitated by different triggers.[7,8] These data raise the subsequent questions: What mechanisms are at the core of large-scale network abnormalities? How the reorganization of the commonly abnormal

*Corresponding author: Dr. Kristina Simonyan, Massachusetts Eye and Ear, Department of Otolaryngology, 243 Charles Street, Suite 421, Boston, MA 02493; kristina_simonyan@meei.harvard.edu

Funding agency: This study was funded by Grant R01NS088160 to K.S. from the National Institute of Neurological Disorders and Stroke, National Institutes of Health.

Relevant conflicts of interests/financial disclosures: Nothing to report.

Received: 13 April 2018; **Revised:** 19 June 2018; **Accepted:** 25 June 2018

Published online 27 September 2018 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.97

dystonic network is specialized to cause clinically different forms of TSFD, such as writer's cramp (WC) and spasmodic dysphonia (SD)? What are the finer grained specializations of a dystonic network necessary for the development of distinct symptomatology while affecting the same muscle group, such as in WC versus musician's focal hand dystonia (MFHD) or SD versus singer's laryngeal dystonia (SLD)?

We hypothesized that manifestation of distinct TSFD symptoms is shaped by selectively altered connectivity of highly specialized brain regions, which form an abnormal network kernel. The latter exerts a critical influence on the reorganization of a larger scale dystonic neural network and underlies altered sensorimotor processing and motor execution during a particular TSFD-affected behavior. To test this hypothesis, we applied graph theoretical analysis to resting-state functional MRI (rs-fMRI) in 4 groups of patients with isolated focal dystonia, including WC, MFHD, SD, and SLD, and compared them to age- and gender-matched healthy individuals and healthy professional musicians. We examined resting-state functional networks because of their high correspondence with the organization of task-related brain networks,[9] which also circumvented the challenges associated with the comparisons of distinctly affected tasks across different forms of TSFD.

Methods

Participant Selection and Grouping

A total of 76 individuals participated in this study (Table 1). The participants were assigned to the following groups to examine:

1. Organization and dystonia-specific distinct alterations of the network kernel in a combined group of 16 TSFD patients (4 patients from each of WC, MFHD, SD, and SLD groups, 45.3 ± 10.8 years old; 8 women/8 men) and 16 healthy participants (8 professional musicians and 8 nonmusicians, 43.9 ± 11.9 years old; 7 women/9 men).
2. TSFD-specific alterations of the network kernel based on the affected body region in 16 hand dystonia patients (8 WC and 8 MFHD, 53.3 ± 10.3 years old; 8 women/8 men) and 16 laryngeal dystonia patients (8 SD and 8 SLD, 54.4 ± 9.9 years; 8 women/8 men).
3. TSFD-specific alterations of the network kernel based on fine motor control skills in 16 musician's dystonia patients (8 MFHD and 8 SLD, 52.2 ± 9.8 years; 4 women/12 men) and 16 nonmusician's dystonia patients without any known motor training (8 WC and 8 SD, 54.8 ± 9.8 years; 5 women/11 men).

No participant had a history of neurological (other than TSFD in patients) or psychiatric disorders. Dystonia was localized to the right hand in WC and MFHD and to the larynx in SD and SLD. All musicians were professionally trained with 30.8 ± 14.1 years of experience in patients with musician's dystonia and 28.1 ± 8.2 years of experience in healthy musicians (see Table 1 for details). None of the patients with nonmusician's dystonia and none of the nonmusician healthy participants had any musical training or skills. This is indicative of a more precise and greater dexterity level that characterizes a higher level of motor learning and execution in musicians than nonmusician participants. Patients receiving botulinum toxin injections participated in the study at least 3 months after their last injection when fully symptomatic. There were no statistical differences in age, gender, handedness, and whenever applicable, years of musical practice, current professional music performance, and disease duration between the groups (Table 1). With the majority of possible biological variables already matched between the examined group, we acknowledge that we were not able to achieve a 1-to-1 matching between the musical instruments in all examined groups because of the challenges with the recruitment of dystonic patients with one of the rarest forms of this disorder. This might represent a limitation of the study as changes in brain networks might differ between instrumentalists and singers.

Written informed consent was obtained from all participants, which was approved by the Institutional Review Board of the Massachusetts Eye and Ear Infirmary (Boston, Massachusetts).

Brain Imaging

Neuroimaging data, including rs-fMRI and high-resolution anatomical images, were acquired on a 3T Siemens Skyra scanner (Erlangen, Germany) equipped with a 32-channel coil (see details of data acquisition in Supplementary Methods). Image preprocessing was performed using FSL[10] and AFNI[11] software following a standard pipeline[12–14] (see details of preprocessing in the Supplementary Methods). Individual regional averages of residual time-series were computed using 212 regions of interest, comprising 142 cortical, 36 subcortical, and 34 cerebellar areas, based on the maximum probability maps and macrolabel atlas.[13,15] The pairwise interaction of regions of interest was estimated using normalized mutual information coefficients.[6,16,17] Group-specific mean networks were constructed by averaging weights of edges present in at least 50% of subject networks[13,18] within each group while controlling for connectedness of the mean graph. To assess the architecture of the constructed functional networks, a community detection analysis was performed following the strategy described earlier[17] (see details of network construction in the Supplementary Methods).

Identification of the Network Kernel

We used a 2-step approach to locate connector hubs, which form a network kernel and influence the

TABLE 1. Participant demographics

	16 TSFD vs 16 healthy contols			16 hand dystonia vs 16 laryngeal dystonia			16 musician's dystonia vs 16 nonmusician's dystonia		
Participants	4 WC 4 SD 4 MFHD 4 SLD	8 NM-HC 8 M-HC	*P*	8 WC 8 MFHD	8 SD 8 SLD	*P*	8 MFHD 8 SLD	8 WC 8 SD	*P*
Age (y; mean ± standard deviation)	45.3 ± 10.8	43.9 ± 11.9	.75	53.3 ± 10.3	54.4 ± 9.9	.77	52.2 ± 9.8	54.8 ± 9.8	.45
Gender	8F/8M	7F/9M	1.0	8F/8M	8F/8M	1.0	4F/12M	5F/11M	.71
Handedness (Edinburgh Inventory)					Right				
Years of musical training (professional musicians)	23.3 ± 9.8	28.1 ± 8.2	.35	35.5 ± 9.2	24.0 ± 13.5	.17	30.7 ± 11.4	N/A	N/A
Active performer (professional musicians)	6Y/2N	8Y	.15	5Y/3N	2Y/6N	.15	7Y/9N	N/A	N/A
Instrument (professional musicians)	2 keyboard 2 strings 4 voice	3 keyboard 2 strings 2 percussion 1 voice	N/A	8 strings/ 8 keyboard	16 voice	N/A	2 keyboard 3 strings 3 percussion 8 voice	N/A	N/A
Disease duration (y; mean ± standard deviation)	12.7 ± 10.6	N/A	N/A	16.4 ± 8.4	13.9 ± 10.5	.46	12.9 ± 9.1	15.1 ± 10.3	.53
Genetic status	Negative for DYT1, DYT6, DYT4, DYT25, arylsulfatase G; No familial history of dystonia								

SLD is an extremely rare form of laryngeal dystonia selectively affecting singing in professional musicians. To date, only 5 patients have been described in the literature.[40] TSFD, task-specific focal dystonia; WC, writer's cramp; MFHD, musician's focal hand dystonia; SD, spasmodic dysphonia; SLD, singer's laryngeal dystonia; NM-HC, nonmusician healthy controls; M-HC, professional musician healthy controls; F, female; M, male; Y, yes; N, no; N/A, not applicable.

architecture of the large-scale network by acting as processing relays, connecting multiple network communities (Fig. 1). First, we identified candidate regions (i.e., nodes) of significant influence in the respective group-averaged networks as quantified by the nodal degree (the number of connected edges) and strength (the sum of connected edge weights). We defined brain regions with both degree and strength at least 1 standard deviation greater than the respective network averages as bivariate hubs. We assessed the contribution of these hubs to intercommunity connections by calculating the nodal participation coefficient, which quantifies each hub's involvement in inter- versus intramodule edges.[13,18] A hub with a participation coefficient 0.3 to 0.75, that is, between 20% and 50% of its links connected to other network communities,[19] was classified as a connector hub.

Next, those connector hubs that were key transfer points in individual network kernels within each group were identified by calculating maximum spanning trees[20] for each subject. The maximum spanning tree of a graph connects all its nodes with the minimum number of maximum-weight edges, which yields a unique result only if every weight-value occurs exactly once within the network.[21] We computed 100 maximum spanning trees for each individual network to account for the possible existence of multiple equivalent branches during tree construction. To quantify the significance of connector hubs across all network kernels within a group, we constructed 100 random graphs/subject and 1 maximal spanning tree for each random network. These trees were used to compute a normalized hub occurrence for every node in the network. Because the determined graph modules represent abstract subsets in a discrete space spanned by the original graph's edges (given a fixed number of nodes), this prevents a direct application of classical statistical inference designs. Instead, we determined the significance of each node's hub occurrence based on how many times it was a bivariate hub across all random versus empirical trees, adjusted for multiple comparisons using a Benjamini-Hochberg false discovery rate correction. We defined connector hubs at a corrected $P \leq .05$ as part of the respective group's network kernel.

Results

Organization and Dystonia-Specific Distinct Alterations of the Network Kernel

The functional network kernels in healthy participants and TSFD patients had largely similar spatial distribution of connector hubs, that is, regions of highest information transfer within a given network. These hubs were embedded in 4 distinct neural communities. Connector hubs in primary somatosensory cortex (bilateral area 3b and right area 2), the left parietal operculum (areas 1 and 4), and the left medial frontal gyrus and right occipital cortex (area 18) were found in the network kernels of both healthy participants and TSFD patients (all within-group $P < .001$; Fig. 2 and Supplementary Table 2).

The network kernel in the healthy participants contained additional connector hubs in the left primary somatosensory cortex (area 1) and cuneus as well as the right primary motor cortex (area 4a), parietal cortex (areas PF, operculum 1), medial frontal gyrus, occipital cortex (area hOC3v), and cerebellum (lobule

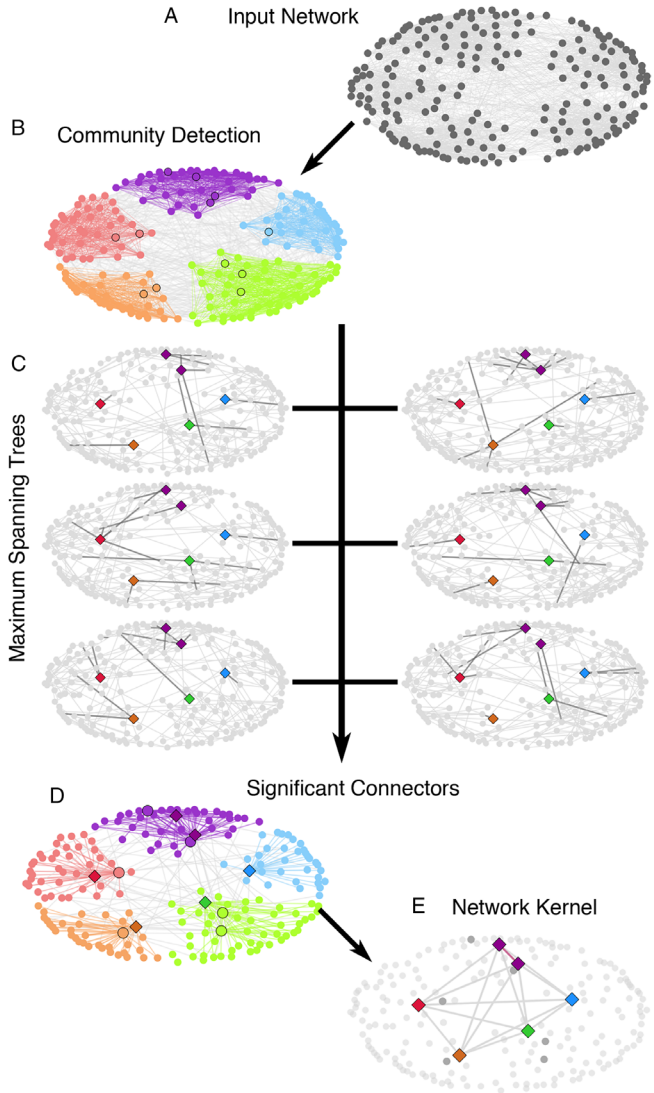

FIG. 1. Identification of network kernels. The input network (A) underwent a community detection (B) by partitioning into connected communities of nodes with maximal number of within-module edges and minimal number of between-module links. Nodes with both degree and strength at least 1 standard deviation greater than the network average and 20% to 50% of their links connected to other network communities were classified as connector hubs (black circles in B). As a next step, a cohort of maximum spanning trees (C) was constructed for the given input network. The significance of each connector hub as central processing relay was assessed by quantifying how many times it was a bivariate hub in a set of null model trees (based on random graphs derived from the input network) versus the empirical tree cohort. Based on this criterion, significant connector hubs (displayed as diamonds in C and D) were identified and formed into the network kernel (E).

VIIa/Cr1; all within-group $P < .047$; Fig. 2 and Supplementary Table 1). These regions did not reach the status of connector hubs to be incorporated into the network kernel of TSFD patients.

TSFD patients displayed a further abnormal set of connector hubs (all within-group $P > .045$; Fig. 2 and Supplementary Table 1), which were not present in the network kernel of the healthy participants. This included right somatosensory (area 1) and parietal cortex (area Ft and operculum 4), left occipital cortex (left area 18 and bilateral middle occipital gyrus) and thalamus (its prefrontal division), which was embedded within the occipital neural community (all within-group $P > .045$; Fig. 2 and Supplementary Table 1). The cerebellar (lobule VIIa/Crus 1) hub switched its hemispheric lateralization from the right representation in healthy participants to the left in TSFD patients ($P < .001$).

TSFD-Specific Alterations of the Network Kernel Based on the Affected Body Region

The presence of dystonia in different body regions (hand vs. larynx) had influenced the global organization of network kernels, which were characterized both by common and distinct dystonia form-specific features. By and large, the network kernels in patients with focal hand dystonia and laryngeal dystonia comprised connector hubs from 3 different neural communities. These were distributed in fronto-occipital, sensorimotor-parietal, and cerebellar regions, respectively (Fig. 3). Both groups of patients had their connector hubs localized in primary somatosensory cortex, including bilateral area 3b, right areas 1 and 2, left parietal cortex (operculum 1 and 4), and cerebellum (lobule VIIA/Crus 1; all within-group $P < .03$; Fig. 3 and Supplementary Table 2).

In addition, each group of patients was characterized by kernel connector hubs, which were specific to either focal hand dystonia (WC and MFHD patients) or laryngeal dystonia (SD and SLD patients) only. The occurrence of additional connector hubs in focal hand dystonia was found in the left primary motor cortex (area 4a) and medial frontal gyrus, right parietal cortex (area 5L, operculum 1 and 4), cerebellum (lobule VIIa/Crus 1 and Crus 2), and bilateral occipital cortex (right area 18 and left middle occipital gyrus; all within-group $P < .001$; Fig. 3 and Supplementary Table 2). Laryngeal dystonia had additional kernel hubs in left primary somatosensory cortex (area 1), bilateral parietal cortex (area 7PC, 7A), and right medial frontal gyrus (all within-group $P < .01$; Fig. 3 and Supplementary Table 2). Thus, the network kernel in focal hand dystonia had greater involvement of sensorimotor and cerebellar connector hubs, whereas the kernel in laryngeal dystonia was distributed around the parietal regions.

TSFD-Specific Alterations of the Network Kernel Based on Fine Motor Control Skills

The network kernels in both musician's and nonmusician's dystonia patients included 4 neural communities, which were centered around sensorimotor-parietal, fronto-occipital, and cerebellar regions (Fig. 4). Independent of musical training, the network kernels in both

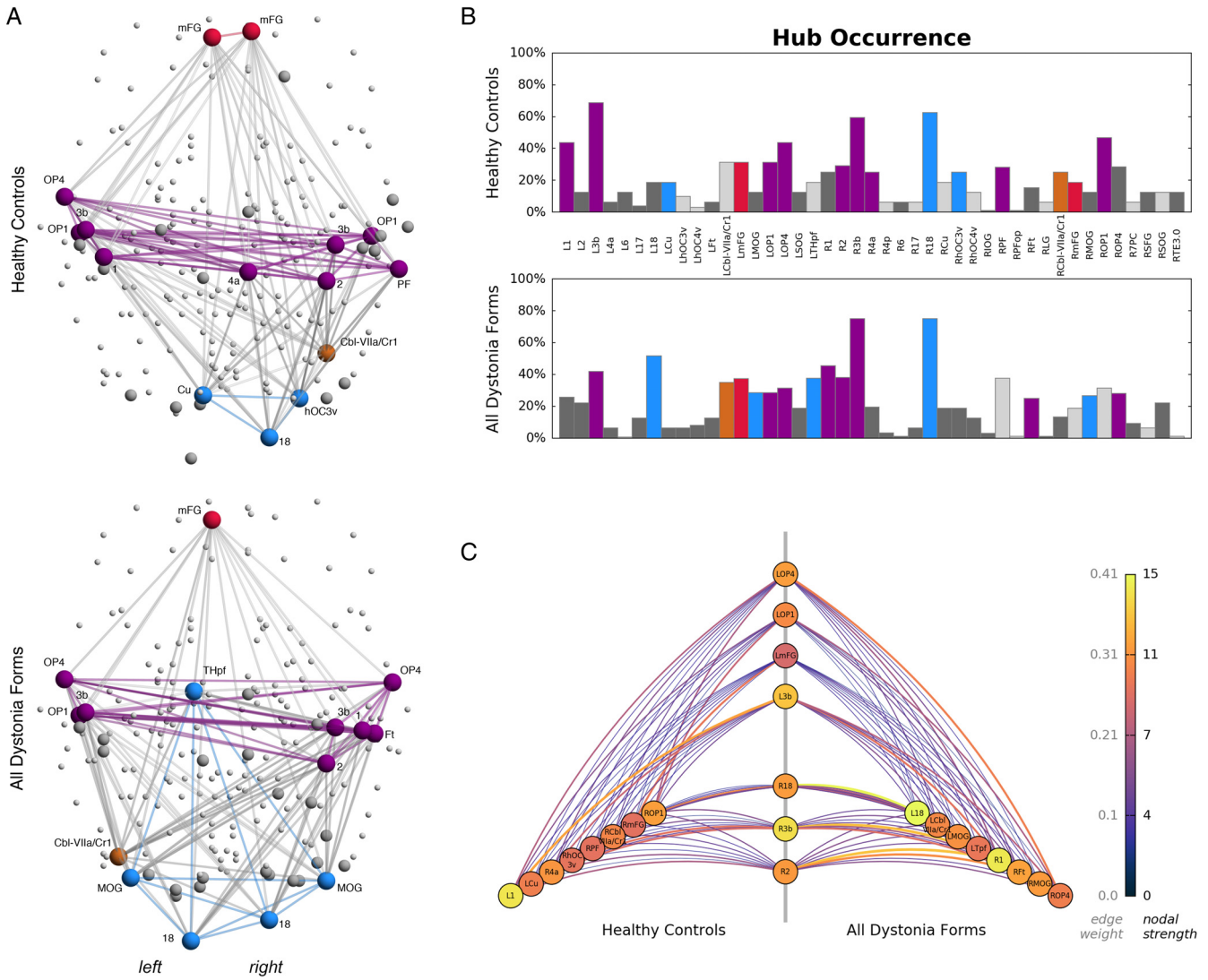

FIG. 2. Organization and dystonia-specific distinct alterations of the network kernel. (A) Axial view showing a 3-dimensional reconstruction of the resting-state network kernel determined in the healthy participants (top) and task-specific focal dystonia patients (bottom) in standard Talairach-Tournoux space. Colored spheres represent kernel hubs with colors indicating network community membership (regions of the same color share the same module affiliation). Intramodular edges use the same color scheme, whereas intercommunity links are rendered in gray. Connector hubs in one group that failed the significance criterion to become kernel members in another group are rendered as dark gray spheres; small light gray nodes illustrate all other regions in the whole-brain parcellation. (B) Bar charts depict the relative frequency of a brain region emerging as a tree-hub across all constructed subject network kernel within each group. Bars corresponding to network kernel regions of the respective group-averaged network are color-coded based on community membership, with bars of nonsignificant connectors shown in dark gray (compare with A). Light gray bars signify regions that were connector hubs in 1 group but failed to achieve this status in the other. (C) Hive plots visualize the connectivity structure of the functional network kernels in the respective groups. The central vertical axis situates kernel hubs shared between the two groups, whereas left and right branches show kernel regions exclusive to the respective group. Regions are color-coded based on their strength in the respective group-averaged networks, where the color of shared kernel hubs corresponds to the average of each region's strength value across the associated mean networks. Link colors illustrate edge weights in the corresponding group-averaged graphs. 1/2/3b/6/17/18 = areas 1/2/3b/6/17/18. 4a/4p, anterior/posterior part of area 4; 7PC, postero-caudal part of superior parietal area 7; Cbl-VIIa/Cr1, cerebellar lobule VIIa Crus 1 (Hem); Cu, cuneus; hOC3v/4v, ventral part of areas hOC3/4; PF, area PF in the inferior parietal cortex; PFop/Ft, opercular part/thin cortical ribbon part of area PF; LG, lingual gyrus; mFG/SFG, medial/superior frontal gyrus; IOG/MOG/SOG, inferior/middle/superior occipital gyrus; OP1/OP4, subdivisions 1/4 of the parietal operculum; TE3.0, temporal area TE3.0; THpf, prefrontal part of the thalamus; L, left, R, right.

patient groups included connector hubs in right primary somatosensory cortex (areas 2 and 3b), left parietal operculum (area 1), left cerebellum (lobule VIIa/Crus 1), and bilateral occipital cortex (area 18; all within-group $P < .001$; Fig. 4 and Supplementary Table 3).

The network kernel in musician's dystonia further included connector hubs in bilateral primary somatosensory (left area 3b and right area 1) and parietal cortex (right area 5L, 7PC, FT, operculum 4, and left operculum 1), left thalamus (its prefrontal division), right occipital cortex (area hOC3v), and cerebellum (lobule VIIa/Crus 1; all within-group $P < .001$; Fig. 4 and Supplementary Table 3). These regions did not form connector hubs in patients with nonmusician's

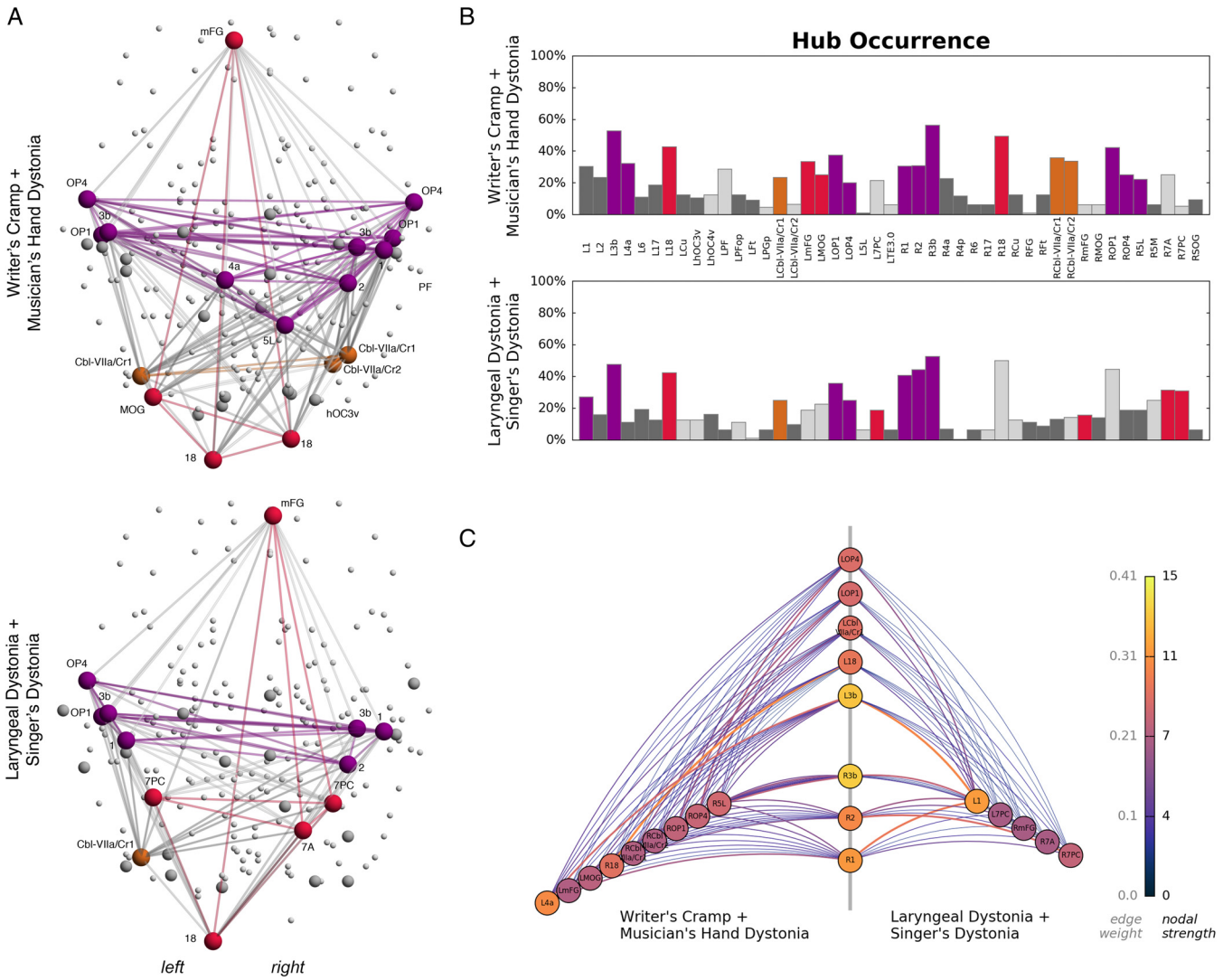

FIG. 3. Task-specific focal dystonia alterations of the network kernel based on the affected body region. (A) Axial view showing a 3-dimensional reconstruction of the resting-state network kernel determined in hand dystonia (top) and laryngeal dystonia (bottom) in standard Talairach-Tournoux space. Colored spheres represent kernel hubs with colors indicating network community membership (regions of the same color share the same module affiliation). Intramodular edges use the same color scheme, whereas intercommunity links are rendered in gray. Connector hubs in 1 group that failed the significance criterion to become kernel members in another group are rendered as dark gray spheres; small light gray nodes illustrate all other regions in the whole-brain parcellation. (B) Bar charts depict the relative frequency of a node emerging as a tree-hub across all constructed subject network kernels within each group. Bars corresponding to network kernel regions of the respective group-averaged network are color-coded based on community membership with bars of nonsignificant connectors shown in dark gray (compare with A). Light gray bars signify regions that were connector hubs in one group but failed to achieve this status in the other. (C) Hive plots visualize the connectivity structure of the functional network kernels in the respective groups. The central vertical axis situates kernel hubs shared between the 2 groups, whereas left and right branches show kernel regions exclusive to the respective group. Nodes are color-coded based on their strength in the respective group-averaged networks, where the color of shared kernel hubs corresponds to the average of each region's nodal strength value across the associated mean networks. Link colors illustrate edge weights in the corresponding group-averaged graphs. 1/2/3b/6/17/18 = areas 1/2/3b/6/17/18. 4a/4p, anterior/posterior part of area 4; 5L/5M, lateral/medial part of superior parietal area 5; 7A/7PC, anterior/postero-caudal part of superior parietal area 7; Cbl-VIIa/Cr1/Cr2, cerebellar lobules VIIa Crus 1/Crus2 (Hem); Cu, cuneus; FG, fusiform gyrus; hOC3v/4v, ventral part of areas hOC3/4; PF, area PF in the inferior parietal cortex; PFop/Ft, opercular part/thin cortical ribbon part of area PF; PGp, posterior part of inferior parietal area PG; mFG, medial frontal gyrus; MOG/SOG, middle/superior occipital gyrus; OP1/OP4, subdivisions 1/4 of the parietal operculum; TE3.0, temporal area TE3.0; L, left; R, right.

dystonia and thus were not part of their network kernel. Instead, patients with nonmusician's dystonia added other regions of left primary somatosensory cortex (areas 1 and 2) and right parietal cortex (area PF, PFcm, PGa, operculum 1) as well as the bilateral medial frontal gyrus, left superior frontal gyrus, and right superior occipital gyrus (all within-group $P < .04$; Fig. 4 and Supplementary Table 3) as connector kernel hubs. Overall, the network kernel of musician's dystonia was characterized by greater involvement of parietal and subcortical (prefrontal thalamus and cerebellum) regions, whereas the network kernel in nonmusician's dystonia showed greater recruitment of the prefrontal executive regions.

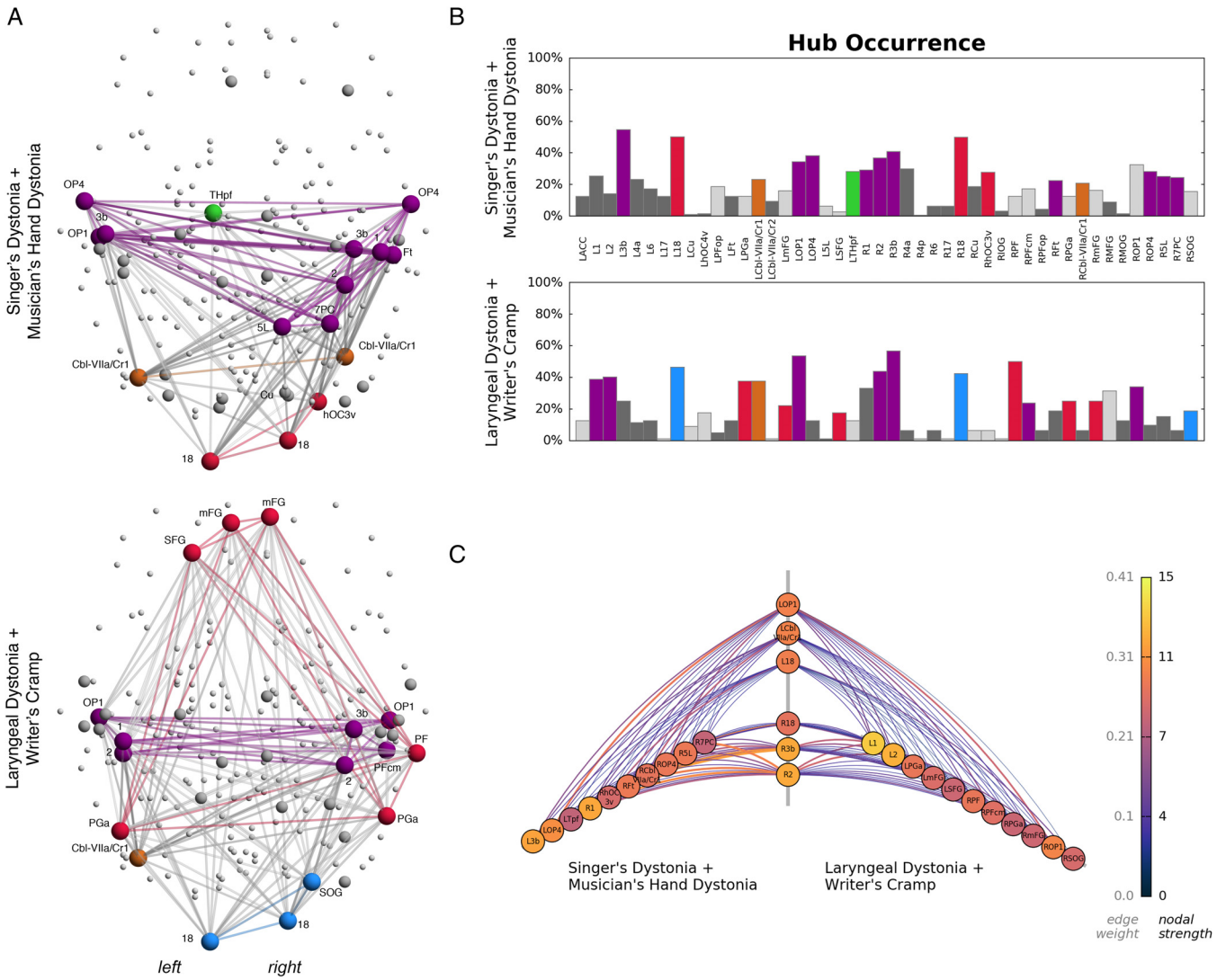

FIG. 4. Task-specific focal dystonia alterations of the network kernel based on fine motor control skills. (A) Axial view showing a 3-dimensional reconstruction of the resting state network kernel determined in musician's dystonia (top) and nonmusician's dystonia (bottom) in standard Talairach-Tournoux space. Colored spheres represent kernel hubs with colors indicating network community membership (regions of the same color share the same module affiliation). Intramodular edges use the same color scheme, whereas intercommunity links are rendered in gray. Connector hubs in 1 group that failed the significance criterion to become kernel members in another group are rendered as dark gray spheres; small light gray nodes illustrate all other regions in the whole-brain parcellation. (B) Bar charts depict the relative frequency of a node emerging as a tree-hub across all constructed subject network backbones within each group. Bars corresponding to network kernel regions of the respective group-averaged network are color-coded based on community membership with bars of nonsignificant connectors shown in dark gray (compare with A). Light gray bars signify regions that were connector hubs in 1 group but failed to achieve this status in the other. (C) Hive plot visualize the connectivity structure of the functional network kernels in the respective groups. The central vertical axis situates kernel hubs shared between the 2 groups, whereas left and right branches show kernel regions exclusive to the respective group. Nodes are color-coded based on their strength in the respective group-averaged networks, where the color of shared kernel hubs corresponds to the average of each region's nodal strength value across the associated mean networks. Link colors illustrate edge weights in the corresponding group-averaged graphs. 1/2/3b/6/17/18 = areas 1/2/3b/6/17/18. 4a/4p, anterior/posterior part of area 4; 5L, lateral part of superior parietal area 5; 7PC, postero-caudal part of superior parietal area 7; ACC, anterior cingulate cortex; Cbl-VIIa/Cr1/Cr2, cerebellar lobules VIIa Crus 1/Crus2 (Hem); Cu, cuneus; hOC3v/4v, ventral part of areas hOC3/4; PF, area PF in the inferior parietal cortex; PFcm/PFop/Ft, columnata mangnocellularis subdivision/opercular part/thin cortical ribbon part of area PF; PGa, anterior part of inferior parietal area PG; mFG/MFG/SFG, medial/middle/superior frontal gyrus; THpf, prefrontal part of the thalamus; IOG/MOG/SOG, inferior/middle/superior occipital gyrus; OP1/OP4, subdivisions 1/4 of the parietal operculum; L, left, R, right.

Discussion

We identified the aberrant functional network kernel that underlies abnormal regional connectivity and influences dystonic activity in different forms of TSFD. Our 3 principal findings are (1) when compared with healthy participants, motor and somatosensory cortical areas are abnormally recruited into the network kernel across different TSFD forms; (2) dependent on the affected body region, the TSFD network kernel is characterized by distinct aberrant functional specializations involving motor execution in hand dystonia and sensorimotor processing in laryngeal dystonia; and (3) dependent on TSFD-affected motor skills, the network kernel

exhibits marked variations in its functional architecture, such as it is associated with alterations of motor execution and sensorimotor integration in musician's dystonia and cortical motor planning in non-musician's dystonia.

Organization and Dystonia-Specific Distinct Alterations of the Network Kernel

The network kernel comprised connector hubs, which, by definition, are highly influential brain regions that display diverse connectivity profiles across several neural communities in a network.[22] Different forms of TSFD showed commonly abnormal recruitment of connector hubs and, thus, abnormal organization of the network kernel. These alterations included both losses of connector hubs that contributed to the network kernel in healthy participants as well as gains of additional connector hubs that were not part of the normal network kernel. This reorganization mostly involved primary sensorimotor and inferior parietal cortices, which suggests core abnormalities in embedding sensorimotor processing and feedback loops as a common pathophysiological trait of different TSFD forms.

Another change in the dystonic network kernel was a gain of the left thalamus (its prefrontal subdivision) as a connector hub, which was not present in healthy participants. However, the output cortical region of this thalamic subdivision, the prefrontal cortex, was downgraded from a bilateral representation in the normal network kernel to only left-sided representation in the dystonic kernel. These findings may indicate abnormal entrainment of learning reinforcement significance of motor actions in TSFD.[23] It is important to note that learning reinforcement is also highly dependent on motor cortex and subcortical structures, such as the ventral striatum and amygdala.[24–26] Among these, the motor cortex was degraded from being a connector hub in TSFD, which points to further decoupling within the prefrontal circuitry, leading to altered consolidation of motor programs. The striatum and amygdala did not reach the status of connector hubs to be included into the network kernel in either the healthy participants or TSFD patients. This may have to do with the level of governance and influence one structure exerts over the other within a given network and the fact that not all regions constituting a network, despite being crucial, ought to fulfill the role of a connector hub.

The dystonic kernel was further characterized by the emergence of bilateral occipital hubs, which were not part of the normal kernel. Although the importance of this region in the pathophysiology of dystonia is not yet clear, visual cortex is a critical site for decoding somatosensory stimuli.[27] Several studies have demonstrated that visual discrimination of somatosensory stimuli is abnormal in dystonia and that this feature potentially represents an intermediate endophenotype of the disorder.[14,28] Although its underpinning mechanisms are not fully understood, our findings suggest that the formation of abnormal network kernel hubs in the occipital cortex and prefrontal thalamus, latter with wide-ranging projection system to the occipital, parietal, and prefrontal areas, may contribute to abnormal somatosensory processing, sensorimotor integration, and decision making during visual discrimination of somatosensory stimuli.

Finally, TSFD network was characterized by a change in the hemispheric representation of some kernel hubs (ie, primary somatosensory area 1 and cerebellar lobule VIIa/Crus 1), which switched their normal hemispheric lateralization in TSFD patients. This change is unlikely to be associated with the lateralization of dystonic symptoms because the TSFD group had a balanced representation of patients with and without lateralized symptoms (ie, right-hand muscles affected WC and MFHD; bilateral laryngeal muscles affected in SD and SLD). Earlier imaging studies in patients with focal hand dystonia and laryngeal dystonia have shown that not only left-hemispheric regions are abnormal but also right fronto-parietal regions are heavily affected.[4,29] Furthermore, our recent study of large-scale functional networks in dystonia has demonstrated a loss of normal hemispheric asymmetry of neural community structure across different forms of focal dystonia, including both task-specific and non-task-specific forms.[7] It appears that larger scale alterations of lateralization in brain activity and connectivity in TSFD may be auxiliary to alterations in hemispheric lateralization of its network kernel.

Overall, with much evidence pointing to dystonia as a functional network disorder,[6,7,30] our findings reveal that abnormal network kernel is at the core of this pathophysiological organization. Given the high importance of connector hubs in the architecture of any network[22] and the fact that abnormal gains of kernel hubs and changes in their hemispheric lateralization did not apparently counterbalance the loss of kernel hubs to attenuate dystonic symptoms, we suggest that alterations of network kernel hubs may likely represent an endophenotypic rather than compensatory trait in this disorder.

TSFD-Specific Alterations of the Network Kernel Based on the Affected Body Region

We found that the presence of dystonic symptoms in a specific body part may shape brain networks through abnormal expression of specialized functional imprints in the respective network kernel. A shared characteristic of both hand and laryngeal TSFDs was the abnormal placement of key sensory processing regions within the functional network kernel, which again indicates the

aberrant control of sensory processing as a pathophysiological trait independent of symptom manifestation.

In addition, more specific characteristics of the network kernel observed in the laryngeal dystonia included the recruitment of superior parietal areas and their consolidation into a single community with frontal and occipital cortices. The superior parietal cortex was shown to be a pivotal component of higher order sensorimotor processing,[31,32] merging auditory and visual streams.[33,34] Thus, the inclusion of these areas into the network kernel in laryngeal dystonia may suggest a pronounced abnormal functional imprint of sensorimotor processing mechanisms onto their baseline network activity.

The functional network kernel of hand dystonia spanned key areas of the central motor control system, including the primary motor cortex and cerebellum. Together with aberrant motocortical activity and connectivity in patients with hand dystonia reported earlier,[35,36] the overrepresentation of motor execution regions in the functional network kernel, as observed here, suggests an abnormal influence of motor command management on the baseline information flow within the large-scale brain network.

Taken together, the abnormal representation of sensory processing regions was common to the network kernels in both laryngeal and hand dystonia. In addition, a distinct feature of the laryngeal dystonia kernel was a propensity for sensorimotor processing, whereas the hand dystonia kernel was characterized by a predisposition for motor mismanagement.

TSFD-Specific Alterations of the Network Kernel Based on Fine Motor Control Skills

As the neural demands increase with the increased motor training and skills, differences in the network kernels of musician's and nonmusician's dystonia reflected symptom-specific deviations in architecture. Notably, the nonmusician's dystonia kernel lost some hub regions in a key component for sensory integration, the left primary somatosensory cortex, but had an overrepresentation of the bilateral inferior parietal cortex. The latter was embedded in a network associated with perceptive and sensorimotor cognition[37] via strong functional coupling with superior parietal and prefrontal cortices. Thus, nonmusician's TSFD was characterized by impaired sensory integration along with abnormally enhanced sensorimotor planning and executive control.

The network kernel in musician's dystonia was shaped by a loss of hubs in the inferior parietal cortex and the gains in superior parietal areas, which were heavily interconnected with kernel hubs in the bilateral primary somatosensory cortex and parietal operculum. The left prefrontal thalamus was decoupled from other neural communities as well as its major cortical target, the prefrontal cortex, which was lost as a kernel hub. In addition, bilateral cerebellar representation within the musician's network kernel formed a central coupling relay establishing strong connections to primary somatosensory areas and the parietal cortex. Consistent with an earlier study showing the relevance of these structures for training and reinforcement learning in healthy musicians,[38,39] our findings indicate that such reorganization of the network kernel may have a direct impact on abnormal sensorimotor integration and retaining motor skills within the motor execution system that is specific to the pathophysiology of musician's dystonia.

Conclusions

In summary, although it is still unclear whether the cascade of dystonic abnormalities is set off by alterations in cortical or subcortical regions, a common feature of the TSFD pathophysiology involves disorganization of its network kernel, which propagates further to larger scale abnormalities of functional activity and connectivity. TSFD symptom distribution was associated with abnormal specializations of network kernels, characterized by propensities for sensorimotor processing in laryngeal dystonia and motor control management in hand dystonia. The level of affected skilled motor behavior shaped the topological structure of its network kernels, such as musician's dystonia was characterized by aberrant interactions between sensory and motor execution systems and nonmusician's dystonia showed abnormal integration of sensory feedback into motor planning and executive control systems.

Acknowledgments: We thank Estee Rubien-Thomas, BA, Hailey Huddleston, BA, Rebecca Scharf, BA, and Azadeh Hamzehei Sichani, MA, for their help with subject recruitment and imaging data acquisition; Andrew Blitzer, MD, DDS, and Steven Frucht, MD, for patient referrals; and Giovanni Battistella, PhD, for help with image preprocessing.

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Supporting Data

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