Sex differences in cortical and subcortical recruitment during simple and complex motor control: An fMRI study

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In this study, we compared brain activation patterns in men and women during performance of a fine motor task, in order to investigate the influence of motor task complexity upon asymmetries of hemispheric recruitment. Thirty-three right-handed participants (17 males, 16 females) performed a self-paced finger-tapping task comprising three conditions of increasing complexity with both the dominant and the non-dominant hand. Imaging results demonstrated significant sex differences in brain activation patterns. While women showed significantly larger activation of ipsi- and contralateral task-related cortical areas than men, men exhibited significantly stronger subcortical activation in striatal regions. The observed activation differences may reflect sex differences in control of voluntary motor skills related to differential emphasis upon cortical and subcortical correlates of motor sequence processing, as well as differences in hemispheric recruitment, by means of which men and women can nevertheless achieve comparable motor performance.
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Introduction

Men and women exhibit pronounced differences in motor skills. Men show superior performance in gross motor skills, such as throwing and targeting, while women usually outperform men in fine motor skills (Hall and Kimura, 1995; Nicholson and Kimura, 1996; Halpern, 1997). Reasons for these differences could be related to either anatomical sexual dimorphisms in a number of brain areas (e.g. Swaab et al., 2001; Aboitiz et al., 1992; Allen et al., 1991; Kulynych et al., 1992; de Courten-Myers, 1999), including motor cortex (Amunts et al., 2000), or to dissimilarities in the functional organisation of the brain.

A number of studies showed differences in functional cerebral asymmetries for various cognitive functions like language, memory, or spatial abilities between men and women. In general, it appears that women are less lateralized than men for a variety of functions (e.g., Hausmann et al., 1998, 2002; Hausmann and Güntürkün, 1999; Shaywitz et al., 1995; Vogel et al., 2003; for a review see Hiscock et al., 1994; McGlone, 1980; Voyer, 1996). Imaging studies revealed sex-specific cortical activation patterns during mental rotation (Jordan et al., 2002) and language tasks (Shaywitz et al., 1995; Kansaku et al., 2000; Kansaku and Kitazawa, 2001). Although these findings are still under discussion (Sommer et al., 2004), it should be noted that the vast majority of studies that found sex differences in functional cerebral asymmetries observed larger lateralization in men.

With regard to motor control, functional cerebral organization appears to be strongly affected by the complexity of the required motor program. Functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies (Colebatch et al., 1991; Pulvermüller et al., 1995; Roland et al., 1980; Rao et al., 1993; Seitz and Roland, 1992; Solodkin et al., 2001) showed that during simple finger-tapping hemispheric asymmetry is increased, i.e. there is predominantly unilateral activation of the contralateral hemisphere controlling the tapping hand. In more complex finger-tapping tasks, however, hemispheric asymmetry decreases due to an additional recruitment of the hemisphere ipsilateral to the tapping hand (Rao et al., 1993; Solodkin et al., 2001). This tendency appears to be stronger when tapping with the non-dominant hand, thus it is stronger in right-handers with left-handed movements and in left-handers with right-handed movements (Cramer et al., 1999; Verstynen et al., 2005). Moreover, left-handers appear to exhibit stronger bilateral activation than right-handers (Solodkin et al., 2001). In contrast to imaging data, the actual performance of the hands is less asymmetric. Here, the dominant hand excels over the subdominant only slightly in simple finger tapping. Only in more complex motor sequencing tasks a higher functional superiority of the dominant hand can be observed

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(Borod et al., 1984; Provins and Magliaro, 1993; Bryden, 2000). However, one recent study varied the complexity within a finger-tapping paradigm and found a stronger asymmetry in a simple (index-) finger tapping than in complex (sequence of four fingers) tapping (Hausmann et al., 2004). Taken together, the behavioral and imaging data indicate that in simple motor tasks, in particular when performed with the dominant hand, mainly contralateral activation is sufficient for successful performance. In more demanding tasks with higher complexity of the tapping sequence and/or involvement of the non-dominant hand, both cerebral hemispheres are active.

Despite the well-known sex differences in motor skills and the sexual dimorphism of the motor cortex (Amunts et al., 2000), the relationship of motor task complexity and sex-specific functional cerebral organisation has rarely been investigated. Therefore, this study investigates the influence of motor task complexity upon asymmetry of hemispheric recruitment in women and men. We varied motor task complexity in a self-paced finger-tapping task with three conditions of increasing complexity. We used fMRI imaging to measure the blood oxygen level-dependent (BOLD) contrast in the brains of male and female right-handed participants during motor performance with the dominant and the non-dominant hand, while at the same time registering behavioral parameters of motor performance. Pertaining to the findings of lower female lateralization for various functions, we expected women to show overall stronger bilateral and/or ipsilateral activation than men. In particular, activation increases with sequence complexity previously found in posterior parietal areas (Haaland et al., 2004; Harrington et al., 2000) were expected to be more bilaterally and/or ipsilaterally organized in women than in men. Since men usually exhibit a higher tapping rate than women (Ruff and Parker, 1993; Kimura, 1999) and some studies proposed a correlation between tapping rate and activation in motor-related brain regions (Kastrup et al., 2002; Blinkenberg et al., 1996), we expected a generally higher activation level of these regions in men than in women.

Materials and methods

Participants

Thirty-three healthy participants (mean age 24.3 years, SD 5.26 years, range 18–45 years), with no history of neurological disease, took part in this study after giving informed consent. (17 men, mean age 23.5 years, SD 4.27 years; 16 women, mean age 25.8 years, SD 6.44 years). All participants were right-handed as defined by positive scores in the Edinburgh Handedness Inventory (EHI; Oldfield, 1971). The protocol was approved by the local ethics committee of the Ruhr-University Bochum. The handedness of all participants was assessed with the Edinburgh Handedness Inventory which yields a laterality index ranging from −100 for maximum left-handedness to +100 for maximum right-handedness. The mean laterality index was +77.66 for women (SD=24.04, ranging from +33 to +100) and +76.82 for men (SD=26.18, ranging from +16 to +100). Moreover, the Hand Dominance Test (Steingrüber and Lienert, 1971) was used. This test consists of three practical drawing tasks the participant has to perform with either hand. The summed performance ratios of the tasks yield a total value ranging from −80 to +170, with positive values indicating superior right-handed performance. The mean

value was +38.64 for women (SD=14.94, range +16 to +66) and +27.0 for men (SD=32.25, range −68 to +63). One male participant had a negative score in the HDT, but due to his positive laterality index of +16 in the EHI he was categorized as an inconsistent right-hander. Since it is known that individuals with fine motor proficiency perform better in finger tapping (e.g. Aoki et al., 2005), and show altered brain activation patterns (Jäncke et al., 2000), all participants were asked about previous experience in fine motor skills that involved tapping movements. Although 10 of the participants (30.3%), i.e. 4 women (25%) and 6 men (35.3%), had some experience in piano-playing and/or the touch-typing system, none of the participants were a professional piano player and/or typist.

Behavioral data acquisition/experimental task

Participants had to perform a self-paced finger-tapping task, adapted from Hausmann et al. (2004), on fMRI-ready optical response keyboards equipped with four buttons each (Lumitouch, Photon Control Inc., Canada) with a special key layout for the non-dominant and the dominant hand, respectively. Tapping complexity increased in the three task conditions: in the 'simple' condition, participants had to press one button only with their index finger as quickly as possible. In the 'complex 1' condition, participants had to press the four buttons repeatedly in the following sequence: index finger, middle finger, ring finger, pinky finger (finger sequence: 2,3,4,5), again as fast as possible while avoiding errors. In the 'complex 2' condition, the tapping sequence was: index finger, ring finger, middle finger, pinky finger (finger sequence 2,4,3,5). To prevent prompting a verbal coding strategy for complex task conditions, we instructed participants by simply demonstrating the sequences without labelling or naming the sequence of fingers, i.e. "2-3-4-5" or "2-4-3-5". Participants performed the tasks without prior practice.

We applied a blocked design with 7 tapping phases and 8 rest (baseline) phases of 24 s duration each. Thus, each scan session took 6 min. In total, 6 scan sessions (3 task conditions for each hand) were acquired for each subject.

All prompts indicating the current tapping condition or the rest phase, respectively, were projected onto a screen and presented to the participant via a 45° angled mirror fixed on the head coil; this mirror was adjusted for each participant to enable view of the screen without having to move the head. Prior to scanning, a test image was presented on the screen to ensure that the images were in focus and that the participant could comfortably read the prompts. The response keyboard for the left and the right hand, respectively, was fixed to the scanner bed in a position adjusted individually for each participant, in order to enable participants to conveniently perform the task. Tapping performance was registered by recording the button presses on the Lumitouch keyboard by means of the 'Presentation' software (Neurobehavioral Systems, Albany, CA, USA).

fMRI data acquisition

Data were acquired using a whole body 1.5 T scanner (Magnetom Symphony, Siemens, Germany) equipped with a high power gradient system (30 mT/m/s; SR 125 T/m/s), using a standard imaging head coil. Blood oxygen level-dependent (BOLD) images were obtained with a single-shot SpinEcho-EPI sequence (TR 3000 ms, TE 60 ms, matrix 64×64, flip angle 90°,

Table 1
Motor task performance

		Simple		Complex 1		Complex 2	
		DH	Non-DH	DH	Non-DH	DH	Non-DH
Tapping rate	Men	133.56±3.20	119.56±2.28	123.71±10.54	106.04±6.40	95.71±4.06	85.94±2.58
	Women	125.60±2.20	108.46±2.36	98.16±5.75	89.77±10.43	77.25±4.99	72.09±4.61
Intertap variability	Men	17.99±1.25	27.80±2.38	74.36±6.82	78.58±7.35	75.32±6.05	79.03±7.49
	Women	21.27±1.84	31.82±2.19	76.16±6.87	73.82±6.82	90.99±6.93	105.68±9.64
Error rate	Men	0.00±0.00	0.00±0.00	3.07±0.53	3.28±0.63	3.00±0.34	2.32±0.42
	Women	0.00±0.00	0.00±0.00	2.69±0.57	3.33±1.00	2.44±0.59	2.39±0.57

Mean tapping rate (taps/24 s), intertap variability (ms) and error rates (%) for the dominant (DH) and the non-dominant (non-DH) hand and for men and women in three task conditions (with standard error means). Significant differences between the sexes were found only for tapping rate across all conditions ($F_{(1,32)}=$ 8.45, $p=0.007$). Significant differences between performance of the hands were found for tapping rate ($F_{(1,32)}=36.04$, $p<0.0001$) and intertap variability ($F_{(1,32)}=5.81$, $p=0.02$), both favouring the dominant hand. The tapping rate decreases ($F_{(2,31)}= 41.94$, $p<0.0001$) and intertap variability increases significantly ($F_{(2,31)}=116.37$, $p<0.0001$) when the complexity of the required tapping sequence increases from simple to complex 2.

field of view 224 mm, slice thickness 3.0 mm, 0.3 mm gap between slices, voxel size $3.5×3.5×3.0$ mm^3). We acquired 30 transaxial slices parallel to the anterior commissure – posterior commissure (AC–PC) line. For each series, 120 images were acquired over 6 min. The whole protocol lasted approx. 45 min. Additionally, anatomical images of each subject were acquired using an isotropic T1-3dGE (MPRAGE) sequence (TR 1800 ms, TE 3.87 ms, matrix 256×256, field of view 256 mm, slice thickness 1 mm, no gap, voxel size $1×1×1$ mm^3) with 160 sagittally oriented slices covering the whole brain.

fMRI data analysis

For preprocessing and statistical analysis of the fMRI data we used the Statistical Parametric Mapping (SPM) Software, Version 2 (Wellcome Department of Cognitive Neurology, London, UK)
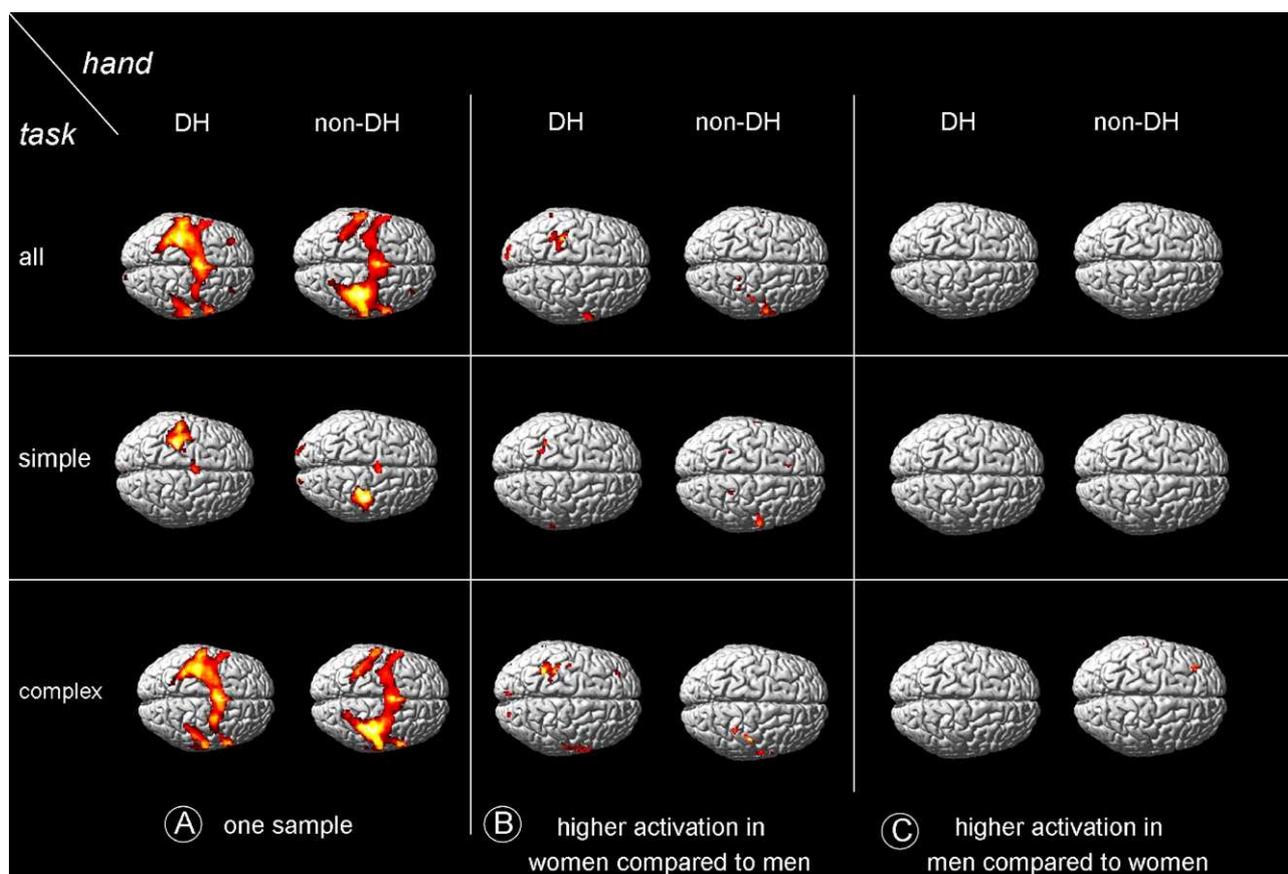
Fig. 1. Overview of cortical areas activated during finger tapping with the dominant (DH) and non-dominant hand (non-DH) for all tasks and during simple and complex tapping separately. (A) Activated areas for the whole group ($p<0.0001$, FWE-corrected, thresholded at T min. >7.67, extent threshold 10 voxels). (B) Areas activated higher in women compared to men. (C) Areas activated higher in men compared to women (all tasks: $p<0.05$, FDR-corrected, thresholded at T min. >3.51; extent threshold 10 voxels; simple and complex tasks separately: $p<0.001$, uncorrected, thresholded at $T>3.55$; extent threshold 10 voxels).

implemented in Matlab (Mathworks, Sherbon, MA). The first 3 images of each fMRI session (120 images), during which the BOLD signal reaches steady state, were discarded from further analysis. Single-subject preprocessing consisted of the following steps: realignment of all images to the first volume, correction for head movement artefacts, normalization into standard stereotaxic space at $2 \times 2 \times 2$ mm^3 using an EPI template provided by the Montreal Neurological Institute, smoothing at 6 mm^3 voxels, and single-subject data analysis. For each participant, contrast images were calculated comparing activation during tapping to the rest phases for each task condition (simple, complex 1, complex 2 with either hand). These individual contrast images were then entered into second level analyses with tapping rate as a covariate. Firstly, task-related brain regions activated during dominant and non-dominant hand tapping in the complete sample were determined using a one-sample t-test with a threshold of $p < 0.0001$ (FWE-corrected), evaluating brain regions activated across all tasks and in the simple and complex tasks separately. Secondly, to identify general sex differences in brain activation with dominant and non-dominant hand tapping, respectively, we conducted a two-sample t-test comparing men and women across all tasks (threshold of $p < 0.05$, FDR-corrected) and in the simple and complex tasks separately ($p < 0.001$, uncorrected). Thirdly, to evaluate task-specific changes in activation, a further two-sample t-test was conducted comparing men and women regarding their brain activation increases from complex 1 to complex 2 tasks with either hand, using a less conservative height threshold ($p < 0.005$, uncorrected). Maxima of significant activation were transformed into Talairach space (Talairach and Tournoux, 1988), anatomical labelling was performed using the Talairach Demon database (Lancaster et al., 1997).

Behavioral data analysis

To evaluate tapping performance, we calculated the tapping rate (mean taps per 24 s each), and the intertap variability (standard deviation of the mean time between successive taps) for all task conditions separately. Only correct taps were included in these analyses, error taps were excluded from analyses. Moreover, we calculated the error rate in percent for all task conditions separately. Group comparisons of behavioral data were analyzed using SPSS 12.0 for Windows.

Results

Motor task performance

Error rates

We calculated the percentage of errors in the tapping conditions separately for each hand and sex. In a $2 \times 2 \times 3$ ANOVA with sex as between-subject factor and tapping hand (dominant, non-dominant) and tapping condition (simple, complex 1, complex 2) as repeated measures, we found a significant main effect of tapping condition ($F(2,31) = 39.67$ $p < 0.0001$). The difference between complex 1 and complex 2 was not significant for the dominant ($F(1,32) = 0.13$, n.s.), and non-dominant hand ($F(1,32) = 2.99$, n.s.) indicating that the main effect of condition resulted from the 'zero errors' result in each of the simple conditions. There were no other significant effects (all $F < 0.75$, n.s.), indicating that neither sex nor tapping hand had an influence on error rate (see Table 1).

Tapping rate

Results from a $2 \times 2 \times 3$ ANOVA with sex as in-between subject factor and tapping hand (dominant, non-dominant), tapping condition (simple, complex 1 and complex 2) as repeated measures showed that the tapping rate was higher with the dominant hand than with the non-dominant hand (main effect of hand, $F(1,32) = 36.04$, $p < 0.0001$). Moreover, tapping rate decreased as complexity increased (main effect of tapping condition, $F(2,31) = 41.94$, $p < 0.0001$). Finally, men tapped more quickly than women (main effect of sex, $F(1,32) = 8.45$, $p = .007$). There were no significant interactions (all $F < 2.45$, n.s.) (see Table 1).

Relation between tapping rate and error rate

We calculated Pearson's correlation coefficient for the relation between tapping rate and error rate. This correlation was not significant for men (all tasks: $r = -0.14$; complex tasks only: $r = 0.17$) or for women (all tasks: $r = -0.20$; complex tasks: $r = 0.11$).

Intertap variability

For intertap variability, a $2 \times 2 \times 3$ ANOVA with sex as between-subject factor and tapping hand (dominant, non-dominant) and tapping condition (simple, complex 1, complex 2) as repeated measures was calculated. The results showed that in both sexes intertap variability was lower with the dominant hand (main effect of hand, $F(1,32) = 5.81$, $p = .02$) and in the less complex conditions (main effect of tapping condition, $F(1,32) = 116.37$, $p < 0.0001$). Men and women did not differ significantly in intertap variability ($F(1,32) = 2.26$, n.s.). Moreover, no interaction approached significance (all $F < 1.29$, n.s.) (see Table 1).

Imaging data

Brain activation patterns of the complete sample during dominant and non-dominant hand tapping

Random-effects analyses of the complete group (one-sample t-test, n=33, $p < 0.0001$, FWE-corrected) with tapping rate as a covariate showed that during tapping with both the dominant and non-dominant hand the simple tapping condition resulted in almost exclusive contralateral activation in pre- and postcentral gyrus, medial frontal gyrus (premotor and primary motor cortex (BA 6, 4), somatosensory cortex (BA 1, 2, 3)), as well as in regions in thalamus and putamen. The complex condition additionally recruited ipsilateral premotor (BA 6), primary (BA 1, 2, 3) and secondary somatosensory (BA 40, postcentral gyrus) areas as well as ipsilateral putamen, and led to predominantly right-hemispheric activation of n. caudatus and lateral globus pallidus. Moreover, in complex tasks we found bilateral activation in inferior and superior parietal lobule (BA 7, 40), insula (BA 13), and regions in the dorsolateral prefrontal cortex in inferior frontal gyrus (BA 9, 44, 45). Bilateral activation in superior temporal gyrus was only seen during dominant hand tapping. Activation patterns across all tasks corresponded largely to the activation in the complex conditions (see Fig. 1; Table 2).

Sex differences in brain activation during dominant and non-dominant hand tapping

The comparison of brain activation patterns of men and women by means of several random-effects group analyses revealed a number of significant differences. First, we pooled the three task conditions (simple, complex 1, and complex 2) with either hand to

Table 2
Brain activation of the complete group during finger-tapping with the dominant (DH) and non-dominant hand (non-DH) for all tasks, and the simple and complex tasks analyzed separately ($p<0.0001$, FWE-corrected, extent threshold 10 voxels)

Activated area	BA	Hem.	All tasks								Simple task								Complex tasks							
			DH				Non-DH				DH				Non-DH				DH				Non-DH			
			x	y	z	t score	x	y	z	t score	x	y	z	t score	x	y	z	t score	x	y	z	t score	x	y	z	t score
Precentral gyrus	4	L	−34	−28	56	24.4					−32	−28	56	17.8					−38	−26	58	20.1				
		R	56	−16	24	12.0	40	−22	62	24.4					40	−18	60	13.5	60	−16	34	11.7	40	−22	62	21.7
	6	L	−34	−10	60	17.2	−38	−10	60	14.4	−24	−22	74	9.0					−34	−10	58	16.6	−56	0	38	12.9
		R	60	−18	44	11.6	32	−6	66	14.0					34	−16	62	11.0	60	−18	42	12.0	30	−14	60	17.5
	44	L									−44	2	10	11.4												
		R					58	12	4	13.4	62	14	12	8.8					52	8	10	13.0				
Medial frontal gyrus	6	L	0	−2	64	18.7	0	−2	58	19.3	0	−2	64	11.9					0	0	62	18.7	−2	−2	64	20.7
		R	8	0	64	15.1									6	0	68	11.5	10	0	64	15.3	8	0	64	15.9
Middle frontal gyrus	6	L	−24	14	62	13.8													−30	−12	68	14.2	−34	−8	62	15.4
		R	52	4	50	9.1													32	−6	66	14.2	32	−6	64	15.8
	8	R	54	6	44	9.0																				
	9	R	58	8	38	9.4	36	44	32	8.9																
	10	L	−32	42	28	9.5																				
Inferior frontal gyrus	9	L	−56	4	36	13.6	−60	8	24	16.4									−58	6	34	13.5	−58	6	34	13.4
	45	L																					−60	8	22	16.9
		R	60	10	20	12.9	60	10	24	14.3									60	10	22	14.5	60	10	24	15.8
	44	L	−56	8	20	16.9													−56	8	18	15.8				
		R	60	14	12	15.1	62	10	16	14.2									56	12	12	13.5	62	10	16	14.2
	47	R	34	20	−2	12.4																				
Superior frontal gyrus	6	L	0	4	54	17.2													0	4	54	17.8				
	9	R	32	42	30	8.5																				
Postcentral gyrus	1	L					−64	−20	28	16.4	−52	−22	52	12.8									−64	−20	28	16.3
		R					54	−20	54	17.5																
	2	L	−56	−22	48	18.8					−56	−22	50	13.1					−58	−20	30	14.7	−62	−22	32	15.8
		R	62	−30	42	9.9													62	−30	42	9.5	42	−36	66	21.9
	3	L	−54	−24	42	18.5	−56	−24	40	14.3	−58	−18	26	8.8					−40	−28	54	19.8	−56	−24	38	15.9
		R	50	−24	38	9.9	40	−22	50	21.4					44	−26	62	12.3	58	−16	24	13.1	40	−34	58	21.3
Postcentral gyrus	5	L																	−38	−46	64	13.1				
	40	L	−50	−24	18	19.4	−58	−22	20	16.4	−58	−22	18	11.5					−58	−22	20	13.8	−58	−22	20	14.2
		R	54	−32	54	9.6	62	−26	18	12.1									40	−40	58	9.1				
	43	R	66	−20	20	12.7	54	−18	18	15.5					52	−18	14	9.9	64	−18	20	13.1				
Inferior parietal lobule	40	L	−44	−38	60	17.1	−40	−40	50	11.6									−44	−38	60	16.0	−34	−44	54	15.9

Region	BA	Side	x	y	z		x	y	z		x	y	z		x	y	z		x	y	z		x	y	z	
		R	42	−36	48	8.4	−34	−40	46	11.2									40	−32	44	11.2				
Superior parietal lobule	7	L																					−24	−54	66	10.1
		R																					30	−50	64	13.5
Insula	13	L	−46	2	2	16.9	−42	4	0	15.9	−48	−24	18	12.1	−42	2	0	9.5	−42	10	−2	12.7	−46	−38	24	11.1
		R	42	10	−2	12.9	50	−22	22	15.3					46	−22	18	10.0	50	10	4	11.6	50	−22	22	13.4
	40	L																	−50	−22	18	15.2				
Superior temporal gyrus	21	R	60	12	0	11.4																				
	22	L	−52	6	2	19.2	−52	4	4	13.7	−52	6	2	9.1					−52	6	4	17.6				
		R	50	8	4	13.2																				
	41	L					−52	−34	14	8.7													−52	−36	14	8.8
	42	R	62	−34	20	10.8													62	−34	20	11.0				
	38	R	56	16	−8	10.5													56	16	−8	8.8				
Transverse temporal gyrus	41	L													−58	−22	20	8.8								
Posterior cingulate	30	R					2	−54	0	12.0													2	−54	0	11.4
Cingulate gyrus	24	L					−10	12	34	12.4	−4	−6	40	9.3												
	32	L	−8	8	40	13.1																				
		R	10	10	40	12.2	6	12	40	13.1																
Cuneus	18	L													−16	−104	8	9.5								
		R	14	−104	6	10.1									18	−104	8	9.5								
	30	L																								
Middle occipital gyrus	18	L													−26	−94	6	9.7								
Lingual gyrus	17	R									6	−94	−8	9.4												
Thalamus, v. lat. N.		L	−18	−16	20	11.9																				
		R																					16	−16	8	12.5
Thalamus v. post. lat. n.		L	−16	−20	8	14.8					−16	−18	2	11.4												
		R					16	−18	6	14.6					18	−18	4	9.4								
Thalamus v. ant. N.		R	14	−4	6	8.8													14	−4	6	8.6				
Thalamus		L																	−14	−12	0	11.4				
		R	16	−8	6	8.6																				
n. caudatus	body	R	16	−16	20	11.8													16	−16	20	10.6	14	−12	20	9.9
Lateral globus pallidus		L	−18	−6	−2	11.7													−18	−6	−2	11.5				
		R					24	−8	2	13.2									18	−4	−2	10.0	18	−4	−2	12.1
Medial globus pallidus		R	16	−4	−6	10.0																				
Putamen		L	−26	−2	8	15.0	20	−6	−2	12.7	−28	0	−8	9.1					−26	−2	10	13.2				
		R	22	8	4	10.7	26	−2	6	12.4					28	−4	−2	9.1	22	6	4	10.8	26	2	6	11.7
Claustrum		L	−30	18	4	12.1																				
		R	30	2	12	9.0																				

BA: Brodmann area; *x, y, z*: MNI coordinates. Table shows the coordinates of local peak activation for the listed brain regions.

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Fig. 2. Sex differences in brain activation during finger tapping with the dominant (DH) and non-dominant (non-DH) hand, shown on coronal slices for all tasks ($p<0.05$ FDR-corrected, thresholded at T min. >3.51; extent threshold 10 voxels), and the simple and complex conditions analyzed separately ($p<0.001$, uncorrected, thresholded at $T>3.55$; extent threshold 10 voxels). Areas of higher activation in women compared to men are displayed in red–yellow, areas of higher activation in men compared to women are shown in blue–green.

compare overall brain activation in men and women across all tasks during dominant and non-dominant hand tapping (two-sample t-test, $p < 0.05$, FWE-corrected, covariate: tapping rate; see Figs. 1 and 2; Table 3). In a second comparison, we distinguished between tapping the simple and the complex conditions with either hand to account for the difference between conditions (one finger vs. four fingers with complex sequences) (two-sample t-test, $p < 0.001$, uncorrected, covariate: tapping rate; see Fig. 2; Table 4). In the following, the results of these two comparisons are reported.

Areas activated stronger in women than in men. When tapping with the dominant hand, women showed higher activation than men in contralateral precentral and postcentral gyrus (primary motor cortex and somatosensory cortex (BA 4, 2, 3)), in ipsilateral premotor cortex (BA 6), as well as in contralateral parietal cortex (postcentral gyrus, inferior parietal lobule, insula (BA 40, 5) and transverse temporal gyrus. Moreover, women showed stronger activation of bilateral posterior and ipsilateral anterior cingulate regions (BA 29, 24, 31), ipsilateral insula (BA 13), as well as of bilateral thalamus. All these activations were also observed in the complex tapping conditions alone, with the exception of cingulate regions and ipsilateral thalamus, which were in turn only evident

in the pooled dominant-hand conditions. Additional areas where significant activation was seen only in the dominant-hand complex conditions were ipsilateral pre- and postcentral gyrus (BA 6, 3) bilateral middle temporal gyrus (BA 39), and contralateral superior temporal gyrus (BA 22). In the simple tasks alone, women showed higher activation than men in contralateral postcentral gyrus (BA 40), bilateral inferior parietal lobule (BA 40), and ipsilateral transverse temporal gyrus and posterior cingulate (BA 31).

When tapping with the non-dominant hand, the pooled conditions revealed higher female activation in bilateral precentral gyrus (premotor cortex, BA 6), thalamus and insula (BA 40, 13), as well as ipsilateral areas in superior and transverse temporal gyrus (BA 22, 42). Exclusively contralateral activation was found in primary motor (BA 4) and somatosensory cortex (BA 1, 3), and in cingulate cortex (BA 24). In the simple task condition alone, there was exclusively contralateral activation in premotor areas (BA 6) and in bilateral posterior parietal lobe and insula (BA 40), moreover in ipsilateral anterior cingulate (BA 24). Areas activated stronger only in the complex, but not in the simple task were bilateral thalamus and posterior cingulate (BA 31).

An additional region significantly activated only in the pooled data of non-dominant hand tapping was contralateral BA 44. The

Table 3
Comparison of activated brain regions in men and women for all tasks, and both the dominant (DH) and non-dominant hand (non-DH) ($p < 0.05$ FDR-corrected, extent threshold 10 voxels)

All tasks			DH									Non-DH							
Activated area	BA	Hem.	Higher activation in									Higher activation in							
			Women				Men				Women				Men			
			x	y	z	t score	x	y	z	t score	x	y	z	t score	x	y	z	t score
Precentral gyrus	4	L	−34	−34	62	5.39												
		R									38	−18	38	4.67				
	6	L									−44	−12	38	4.27				
		R	60	−2	10	5.08					60	−6	34	5.38				
	44	R									52	0	10	4.37				
Postcentral gyrus	2	L	−42	−26	46	4.05												
	3	L	−22	−38	70	4.22												
		R									46	−22	62	4.82				
Paracentral lobule	3	R									20	−38	58	4.61				
Postcentral gyrus	5	L	−32	−46	64	3.95												
Inferior parietal lobule	40	L	−62	−48	24	3.75												
Insula	40	L	−48	−26	16	6.81												
		R									48	−24	14	4.17				
	13	L									−44	−26	18	4.63				
		R	56	−34	18	3.84												
Transverse temporal gyrus	42	L	−60	−12	12	3.75					−60	−14	12	5.08				
Superior temporal gyrus	22	L									−60	−6	8	4.23				
Middle temporal gyrus	39	L													−32	−54	28	5.65
Posterior cingulate	29	L	−4	−46	8	4.37												
		R	8	−46	16	3.94												
Cingulate gyrus	24	R									14	−20	46	4.49				
	31	R	16	−30	40	3.89												
Cuneus	18	L	−10	−100	6	4.6												
Middle occipital gyrus	18	L	−24	−98	18	4.23												
Inferior frontal gyrus	9	R	52	0	26	3.6												
Amygdala		R	26	−8	−12	4.32												
Thalamus		L	−8	−26	0	4.21									−12	−30	18	4.76
		R	14	−28	−2	4.1									12	−32	22	4.87
n. caudatus	tail	L													−18	−40	12	4.76

BA: Brodmann area; x, y, z: MNI coordinates. Table shows the coordinates of local peak activation for the listed brain regions.

Table 4
Comparison of activated brain regions in men and women for the simple (A) and complex (B) tasks separately during tapping with the dominant (DH) and non-dominant hand (non-DH) ($p<0.001$, uncorrected, extent threshold 10 voxels)

Activated area	BA	Hem.	DH								Non-DH							
			Higher activation in								Higher activation in							
			Women				Men				Women				Men			
			x	y	z	t score	x	y	z	t score	x	y	z	t score	x	y	z	t score
(A) Simple task																		
Precentral gyrus	6	L																
		R									60	−6	32	4.46				
	43	L									−60	−8	14	4.11				
Postcentral gyrus	40	L	−50	−26	16	4.51												
Inferior parietal lobule	40	L	−38	−44	52	3.77												
		R	68	−38	24	3.55												
Parietal lobe	40	L	−22	−46	54	4.73					−26	−40	58	3.82				
		R									22	−40	58	4.68				
Insula	40	L									−48	−28	18	3.89				
		R									50	−24	14	3.65				
Transverse temporal gyrus	41	R	56	−22	14	3.82												
Middle temporal gyrus	39	L													−44	−76	12	4.91
Cingulate gyrus	24	L									−16	2	38	5.04				
	31	R	14	−28	42	3.97												
Medial frontal gyrus	8	L									−12	28	48	3.98				
n. caudatus	Body	R					18	−20	30	4.42								
							8	−4	28	4.32								
Putamen		L									−20	−2	8	5.15				
		R									24	2	4	3.75				
(B) Complex tasks																		
Precentral gyrus	4	L	−40	−16	56	3.51												
		R									38	−18	38	3.66				
	6	R	60	−2	10	4.39					62	−10	36	3.82				
	44	R	62	10	16	3.76												
Postcentral gyrus	2	L	−40	−28	46	3.85												
	3	L	−34	−34	62	4.24												
		R	60	−20	36	3.63					46	−22	62	5.49				
Postcentral gyrus	5	L	−36	−46	62	4.48												
	40	L	−40	−40	58	4.21												
		R									34	−40	60	4.49				
Inferior parietal lobule	40	L													−60	−22	24	3.85
Insula	40	L	−48	−26	16	5.25												
Superior temporal gyrus	22	L	−62	−46	12	3.63												
	38	L													−54	2	−6	3.92
	39	R					42	−60	28	4.9								
Middle temporal gyrus	39	L	−40	−54	8	3.47									−32	−54	20	4.44
		R	48	−70	8	3.52									36	−58	20	3.68
Anterior cingulate	32	L													−14	40	10	4.06
Posterior cingulate	31	L									−26	−60	18	3.96				
Cingulate gyrus	24	L													−6	−6	24	3.57
	31	R									16	−26	38	3.56				
Cuneus	19	L	−6	−92	32	4.05												
		R	20	−88	34	3.77												
	30	L	−6	−62	6	3.65												
Middle occipital gyrus	19	L	−40	−84	4	3.8												
	37	L	−42	−72	0	3.53												
Middle frontal gyrus	9	L	−32	44	38	3.93									−32	34	28	4.12
	11	L													−42	46	−14	3.99
Inferior frontal gyrus	9	R	52	0	26	3.73												
Superior frontal gyrus	10	R									22	54	12	4.23				
Medial frontal gyrus	10	L													−16	50	8	3.68
Thalamus		L	−8	−16	16	4.06					−4	−26	−2	3.75				
		R									4	−26	0	3.41				

Table 4 (*continued*)

Activated area	BA	Hem.	DH								Non-DH							
			Higher activation in								Higher activation in							
			Women				Men				Women				Men			
			x	*y*	*z*	*t* score	*x*	*y*	*z*	*t* score	*x*	*y*	*z*	*t* score	*x*	*y*	*z*	*t* score
(B) Complex tasks																		
Thalamus, pulvinar		L													−10	−34	16	4.22
		R													14	−32	20	4.79
n. caudatus	Tail	L					−22	−44	16	3.52					−18	−38	12	4.39
	Head	L													−14	26	8	4.03
	Body	L													−8	2	26	3.62
		R	16	−14	20	3.83	14	−22	30	3.99					16	−12	32	3.93
Claustrum		R													26	20	−4	4.08

BA: Brodmann area; *x*, *y*, *z*: MNI coordinates. Table shows the coordinates of local peak activation for the listed brain regions.

only region activated in the complex task conditions with the non-dominant hand, but not appearing in the pooled data was ipsilateral caudate body.

Areas activated stronger in men than in women. For tapping with the dominant hand, pooled conditions showed no brain area to be activated stronger in men compared to women. When analyzing simple and complex tasks separately, however, dominant hand tapping activated ipsilateral (simple) respectively contralateral (complex) n. caudatus in men stronger than in women. Moreover, in complex tasks, a region in ipsilateral superior temporal gyrus (BA 39) showed higher activation in men than in women.

For tapping with the non-dominant hand, pooled data showed significantly stronger activation in men than in women in ipsilateral caudate tail, bilateral thalamus, and in ipsilateral middle temporal gyrus (BA 39). In the simple task alone, higher activation was restricted to this region (BA 39). Areas with significantly higher male activation in the complex tasks alone were ipsilateral

cingulate (BA 24, 32), middle frontal gyrus (BA 9, 11), bilateral caudate body, and contralateral claustrum.

Sex differences in the comparison of the complex 1 and complex 2 conditions

This comparison evaluated areas yielding activation differences between the two sequential tapping conditions. Although 4 fingers are involved in both tasks, the finger sequence in complex 2 is more difficult, as indicated by a greater intertap variability. The comparison between both complex conditions shows those areas that exhibit differential activation increases between men and women in response to increasing task complexity from complex 1 to complex 2 ($p < 0.005$, uncorrected, cluster level: $k = 20$) (see Fig. 3; Table 5).

Areas where men show higher activation than women in the complex 2 task as compared to the complex 1 task. With both dominant and non-dominant hand tapping, men exhibit more

Fig. 3. Sex differences in activation increases in the complex 2 condition as compared to complex 1 ($p < 0.005$, uncorrected, thresholded at $T > 2.74$; extent threshold 20 voxels). Areas of higher activation in women compared to men are displayed in red–yellow, areas of higher activation in men compared to women are shown in blue–green.

Table 5
Areas of higher activation with increasing task complexity – comparison of men and women for activation increases in the complex 2 task compared to the complex 1 task ($p < 0.005$, uncorrected, extent threshold 20 voxels), analyzed separately for the dominant (DH) and non-dominant hand (non-DH)

Activated area	BA	Hem.	DH Areas activated higher in Women				DH Areas activated higher in Men				Non-DH Areas activated higher in Women				Non-DH Areas activated higher in Men			
			x	y	z	t score	x	y	z	t score	x	y	z	t score	x	y	z	t score
Precentral gyrus	6	L													−34	−8	30	4.28
Superior parietal lobule	7	L													−24	−58	38	3.58
		R													36	−70	46	3.52
Inferior parietal lobule	40	L													−46	−38	44	3.87
Parietal lobe	40	R													22	−46	54	4.37
Precuneus	7	L													−22	−66	40	3.27
	19	R													30	−74	36	3.34
Cuneus	17	R					18	−78	6	3.21								
Superior temporal gyrus	42	L					−66	−26	12	3.82								
	22	L					−48	−24	−4	3.37								
	41	R					52	−28	6	3.20								
Middle temporal gyrus	39	R													34	−72	28	3.07
Anterior cingulate	24	L					−16	−14	38	3.52								
	32	L													−22	44	4	3.54
Middle frontal gyrus	11	L													−42	46	−6	3.24
Inferior frontal gyrus	45/46	R													52	30	20	3.16
Hypothalamus		L													−2	−4	−6	3.67
Thalamus		L									0	−18	−2	4.17				
Thalamus, pulvinar		L													−12	−36	14	4.11

BA: Brodmann area; x, y, z: MNI coordinates. Table shows the coordinates of local peak activation for the listed brain regions.

extensive activation increases than women in the complex 2 than in the complex 1 condition. When tapping with the non-dominant hand, the greater activation in men is observed bilaterally in parietal areas encompassing the inferior and superior parietal lobule (BA 7, 40), and precuneus. In the frontal cortex higher activation is observed in regions comprising ipsilateral precentral and middle frontal gyrus (BA 6, 11) and contralateral inferior frontal gyrus (BA 45/56). Furthermore, there are clusters of superior activation in ipsilateral hypothalamus and thalamus and in posterior cingulate.

When tapping with the dominant hand, men show stronger activation increases than women in ipsilateral cuneus (BA 17), bilateral superior temporal gyrus (BA 22, 41, 42) as well as in contralateral anterior cingulate.

Areas where women show higher activation than men in the complex 2 task as compared to the complex 1 task. Activation increases in women compared to men during the complex 2 task compared to the complex 1 task were seen only in ipsilateral thalamus during tapping with the non-dominant hand.

Discussion

The overall brain activation pattern observed is consistent with previous imaging data on finger tapping and sequential finger movements (Rao et al., 1993; Roland et al., 1980; Boecker et al., 1998, Moritz et al., 2000). Although performance did not differ between men and women except for tapping rate, direct comparisons between men and women revealed a number of sex differences in brain activation. Women in general show higher cortical activation than men during tapping with either hand, and they exhibit more ipsilateral activation in motor–task-relevant

regions than men, in particular during finger tapping with the dominant hand. Altogether, as hypothesized, women show stronger bilateral cortical activation. In contrast, men exhibit higher subcortical activation in the basal ganglia. Moreover, in some brain regions, men show stronger increases of cortical activation than women with increasing task complexity.

Women show stronger ipsilateral activation than men

Across most tapping conditions, ipsilateral cortical activation in motor-task related regions is more pronounced in women. There is higher ipsilateral activation, particularly when tapping complex sequences with the dominant hand, in premotor (BA 6) and somatosensory (BA 3) areas; when tapping simple sequences with either hand, there is higher activation in parieto-temporal regions, e.g. the inferior parietal lobule (BA 40), insula, and transverse temporal gyrus (BA 41). In the most demanding conditions, i.e. tapping complex sequences with the non-dominant hand, this sex difference decreases. Here men show higher activation in ipsilateral inferior parietal lobule (BA 40), superior and middle temporal gyrus (BA 38, 39) and medial and middle frontal gyrus (BA 9, 10, 11). The results comparing activation increases from the complex 1 to the complex 2 condition also indicate an activation surplus for men in bilateral inferior and superior parietal lobule, and in ipsilateral middle frontal gyrus during non-dominant hand tapping only.

Taken together, the results indicate that the difference between men and women in ipsilateral activation of task-related regions decreases with increasing task complexity and when the non-dominant hand is used. When tapping a complex sequence with the non-dominant hand, men recruit left-hemispheric areas to an even larger extent than women. It appears therefore that

women already recruit ipsilateral regions in less demanding task conditions.

Previous studies reported that ipsilateral activation in motor tasks is stronger when the non-dominant hand is used (Cramer et al., 1999; Verstynen et al., 2005). These findings are in line with the notion that the left hemisphere appears to be dominant for fine motor skills performed with either hand (Serrien et al., 2006), particularly in right-handers. Thus, ipsilateral activation in a right-handed sample during non-dominant-hand tapping – as observed in this study – was to be expected. Since previous studies, however, did not evaluate activation patterns of male and female participants separately, our results extend the existing findings by demonstrating a female-specific ipsilateral activation pattern.

Women show stronger activation of parietal and superior temporal regions

Higher female activation in parietal regions, in particular inferior parietal lobule and insula (BA 40) and superior temporal regions (BA 22, 41, 42) during almost all tapping conditions with either hand suggests that women rely more heavily upon motor imagery and temporal sequence computations than men. Activation of inferior parietal lobule is found during motor sequence learning and retrieval (Lafleur et al., 2002). Activation of the intraparietal sulcus and the inferior parietal lobule was observed in successful imagery of a finger tapping (Hanakawa et al., 2003) or hand movement (Lacourse et al., 2005) motor sequence, moreover during later phases of learning and retrieval of a visuomotor sequence (Sakai et al., 1998). Significant activation of these regions during finger tapping might thus reflect learning and remembering the tapping sequence by imagining sequential movements of the fingers.

In agreement with our results, activation of superior temporal gyrus has repeatedly been found in motor tasks that require temporal processing of movements. This structure is thought to be related to temporal sequence control (Ullen et al., 2005) and seems to be particularly involved in the organisation of rhythmic sequences (Bengtsson et al., 2005), presumably delivering rhythmic control (Ullen et al., 2003). A study using syncopation tasks found that activity in superior temporal gyrus was no longer observed after extensive practice, possibly indicating a reduced demand upon attention and sensory feedback with practice (Jantzen et al., 2002).

The generally higher ipsilateral cortical activation in females is in line with findings reporting that women show less lateralization in a variety of functions (Hausmann et al., 1998, 2002; Hausmann and Güntürkün, 1999; McGlone, 1980; Voyer, 1996) and tend to recruit bilateral areas in various functions, such as language (Shaywitz et al., 1995; Kansaku et al., 2000; Kansaku and Kitazawa, 2001) and spatial cognition (Vogel et al., 2003), where men show more lateralized activation. It is often argued that a reduced lateralization in women might result from larger interhemispheric connectivity via the commissural system. Regions in the posterior part of the corpus callosum that were found to be larger in women than in men are the isthmus (Witelson, 1989; Steinmetz et al., 1992) and the splenium (e.g. De Lacoste-Utamsing and Holloway, 1982; Allen et al., 1991; Davatzikos and Resnick, 1998; Dubb et al., 2003). The isthmus contains interhemispheric fibers connecting the posterior parietal and superior temporal areas (e.g. Hofer and Frahm, 2006; Park et al., 2006), suggesting that a higher bilateral activation of these areas in women might be related to

their stronger interhemispheric connectivity. However, although a larger posterior part of the corpus callosum in females is still discussed controversially – e.g. Luders et al. (2006) did not find any regional thickness increases in women compared to men – the majority of studies that found size differences in the posterior corpus callosum reported this structure to be larger or more bulbous in women than in men.

Women in general also showed more ipsilateral/bilateral activation than men in posterior cingulate regions during finger tapping with either hand. However, considering complex and simple tasks separately, the relation between condition, hand and sex appears to be more complicated. If at all, men show superior recruitment of anterior cingulate regions predominantly during the complex conditions with the non-dominant hand, while women show a higher extent of cingulate activation during finger tapping with the dominant hand.

Concurrent with our results, the anterior cingulate was shown to be involved in motor timing (Rubia and Smith, 2004) as part of a frontostriatal neural timing circuit (Stevens et al., 2006). Other studies observed posterior cingulate activation during self-paced finger tapping, as opposed to externally paced tapping (Schubert et al., 1998), and also while performing a finger-tapping sequence with the previously untrained hand by transfer from the trained hand (Lutz et al., 2001). Superior learning of a fine motor task was found to be associated with posterior cingulate activation (Tracy et al., 2003). Thus, posterior cingulate might be implicated in self-controlled performance of a motor task.

Women show higher cortical activation than men in contralateral task-relevant motor and somatosensory regions

Already in simple tapping, contralateral activation of premotor regions in precentral gyrus (BA 6) and somatosensory-related regions in postcentral gyrus (BA 40) was higher in women than in men during non-dominant and dominant hand tapping, respectively. With increasing task complexity, this stronger contralateral activation was maintained, and extended further to contralateral primary motor regions in precentral gyrus (BA 4) during finger tapping with the dominant hand and primary somatosensory cortex in postcentral gyrus (BA 2, 3) during finger tapping with either hand. Since women's tapping frequency was lower than men's, our findings of higher female contralateral activity in these motor task-relevant regions disagree with our hypothesis and with results reporting a relation of tapping frequency and activation level in brain areas involved in relevant motor and sensory processes (Kastrup et al., 2002; Blinkenberg et al., 1996), indicating that the relation between these regions and tapping performance might be more complex.

Men show stronger striatal activation than women

Men displayed stronger bilateral activation of n. caudatus across all complex conditions with either hand and ipsilaterally in the simple condition with the dominant hand. This is in line with the results of Lehericy et al. (2006) who observed an increase of caudate activation with increasing tapping frequency and sequence complexity. Such a stronger caudate activity in men could explain their overall higher tapping rates (see also Ruff and Parker, 1993; Kimura, 1999). However, it has also been speculated that men's ability to tap faster may be related to a peripheral effect of testosterone upon muscle fibres (Hausmann et al., 2004; Schmidt et

al., 2000), since the size of fast-twitch fibers is influenced by testosterone (Puhl, 1986).

Activation of the basal ganglia, in particular of the striatum, appears to be related to both new learning and automatic motor sequencing performance. Several imaging studies found an activation increase with automaticity (Seitz and Roland, 1992; Doyon et al., 1996; Penhune and Doyon, 2002) and during planning sequences before movement onset (Parsons et al., 2005). Others reported caudate involvement predominantly during new learning, or striatal activation during attended automatic performance (Floyer-Lea and Matthews, 2004; Jueptner and Weiller, 1998). Although some investigations observed a decrease of striatal involvement during early learning (Jueptner et al., 1997; Toni et al., 1998), other studies reported no activation change in automaticity compared to learning (Wu et al., 2004; Jansma et al., 2001). Together, these findings suggest that the striatum may be crucial for long-term storage of well-trained motor sequences (Doyon et al., 2003). In principle, it is thus possible that men's stronger striatal activation, particularly in the complex conditions, might indicate advanced automatization in finger tapping, corresponding also to their higher tapping rate. However, results are still contradictory and possibly only more standardized motor tasks will reveal whether sex differences in cortical versus striatal activation patterns indeed reflect a sex-specific strategy of males towards automatization of repeated motor patterns.

Men show stronger activation increases with increasing task complexity

From the complex 1 to the complex 2 condition, men showed activation increases in fronto-parietal and temporal regions as well as in the thalamus – areas that in general were activated significantly stronger in women than in men. It appears therefore that men recruit these areas. only in the most complex conditions, while women already use these regions lower in the hierarchy of task complexity.

In frontal regions, however, there appears to be a stronger male-specific increase in activation from complex 1 to complex 2. These regions were not among those that were generally more highly activated in women. In men, tapping with the non-dominant hand led to stronger activation increases in ipsilateral middle and contralateral inferior frontal gyrus (BA 11, 45/46). These areas have been found implicated in higher-level motor control/planning during self-paced motor tasks (Johnson-Frey et al., 2005), as well as in sustained action monitoring (Schnell et al., 2007) (dorso-lateral prefrontal cortex), and in temporal control of a learned movement sequence (inferior frontal gyrus, Bengtsson et al., 2004).

Conclusion

In summary, the results of the present study demonstrate that despite comparable tapping performance, men and women exhibit substantial differences in brain activation during motor sequencing control. These differences relate to activation level and conditions of recruitment, with higher activation levels of cortical and subcortical regions in women and men, respectively. According to the model proposed by Doyon et al. (2003), a network consisting of motor cortical regions, parietal regions and striatum is involved during all phases of motor sequence learning and performance, i.e.

acquisition, consolidation, and automatization. The observed sex differences in brain activation might therefore result from a differential emphasis of women and men in recruiting individual network components that are implicated in different aspects of motor-related processing. In general, these findings underline the assumption that similar motor skills can be achieved by a differential, sex-specific functional cerebral organization.

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