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Do Brain Structural Abnormalities Differentiate Separate Forms of Urgency Urinary Incontinence?

Becky D. Clarkson, Derek Griffiths, and Neil M. Resnick

Division of Geriatric Medicine, University of Pittsburgh

Abstract

Aims.—Urgency urinary incontinence (UUI) is a major problem for seniors. The underlying mechanisms of disease and therapy are unknown. We sought structural brain abnormalities that might underlie the functional differences previously observed by functional Magnetic Resonance Imaging in UUI patients versus controls, or among UUI responders vs non-responders to therapy – and thereby reveal potential disease mechanisms and therapeutic targets.

Methods.—Secondary study of a trial of biofeedback-assisted pelvic floor muscle training (BFB) in 60 women (60 yrs) with UUI, plus 11 age-matched continent controls. Brain structural abnormalities were investigated using: (1) white-matter hyperintensities (WMH); (2) diffusion tensor imaging (DTI) to reveal white-matter pathways with impaired integrity; and (3) voxel-based morphometry (VBM) to show regions of atrophy or hypertrophy.

Results.—WMH burden was greater in UUI patients than controls (globally and in superior longitudinal fasciculus and cingulum), suggesting a possible causal connection. WMH burden was unexpectedly greater in responders than non-responders to BFB, and appeared to increase in non-responders but not in responders. DTI revealed even worse integrity of the cingulum than was apparent by WMH. VBM showed parahippocampal atrophy in UUI.

Conclusions.—Many women with UUI have white-matter damage that interferes with pathways critical to bladder control; they can be taught by techniques like BFB to exert stronger control over the bladder. For others, in whom abnormalities of key brain areas are less marked, UUI's cause may reside elsewhere, and therapy targeting these brain centers may be less effective than therapy targeting the bladder or other brain centers.

Keywords

Magnetic Resonance Imaging; White Matter Hyperintensities; Diffusion Tensor Imaging; Voxel-based Morphometry

Introduction

Urgency urinary incontinence (UUI) is a common and troublesome problem. Despite decades of research its cause is not well understood and it remains difficult to treat.¹ We

Corresponding author Becky Clarkson, Geriatric Medicine, University of Pittsburgh, Montefiore Hospital NE547, 3459 Fifth Avenue, Pittsburgh PA, 15213, U.S.A., Telephone +1 412 647 1270.

Registered at clinicaltrials.gov (NCT00177541)

have shown that neither ultrastructural² nor urodynamic³ changes adequately explain the causal mechanism of UUI or its response to behavioral therapy. Others have focused on peripheral abnormalities,⁴⁻⁶ but none of these approaches has identified a cause of UUI or greatly improved treatment.¹

Until recently, the role of the *central* nervous system (CNS) in bladder control has been little investigated. Several investigators have speculated that damage to the connectivity of the brain's voiding control network, manifested as white matter hyperintensities (WMH) on magnetic resonance imaging, might be linked to UUI.⁷⁻⁹ Since UUI occurs mainly in the elderly, however, other physiologic, pathologic, and drug-related changes in the central nervous system and the lower urinary tract may also contribute, hindering interpretation.

Consequently we and others have used *functional* magnetic resonance imaging (fMRI) to investigate brain responses to provocations such as rapid bladder filling. This has led to a working model of CNS control (Fig.1),¹⁰ based on a few key centers: the dorsal anterior cingulate cortex (dACC, concerned with emotion, salience, and urgency); the nearby supplementary motor area (SMA, which contracts the sphincter);¹¹ the medial prefrontal cortex (mPFC, executive control); and the midbrain periaqueductal gray (PAG, linchpin in forestalling or initiating voiding).¹² Other putative centers include the pontine micturition center (PMC, coordinates bladder and sphincter); thalamus (central relay station); insula (maps bladder sensation);¹³ and a parahippocampal-hypothalamic region. These centers and their interconnections seem to be organized into 3 neural circuits, each of which can help to maintain continence, probably by inhibiting the PAG.¹⁰

Clearly, *structural* abnormalities in the connecting pathways might underlie the *functional* abnormalities seen on brain imaging in UUI subjects, and indeed the volume of WMH in the whole brain or in certain individual tracts (e.g. the anterior thalamic radiation, the superior longitudinal fasciculus, and the cingulum) is correlated with the risk or severity of UUI.^{8,14} However, symptoms associated with WMH lesions include impaired mobility, decreased cognition, and depression, each of which may indirectly aggravate incontinence.¹⁵

A few brain-imaging studies of UUI response to therapies such as sacral neuromodulation¹⁶ or bladder relaxant medication¹⁷ have been performed. Overall, responders to these therapies showed brain changes that tended toward normal, as expected.

To examine the issue further we used a different intervention – biofeedback-assisted pelvic-floor muscle training (BFB)^{18,19} – as a probe to reveal functional brain abnormalities that might cause or contribute to UUI. We sought potential predictors and mediators, defined respectively as variables whose baseline value, or whose change from baseline, correlated significantly with therapeutic response and was both clinically significant and biologically plausible.^{3,18} In that study, BFB reduced UUI frequency by more than half in 43% of subjects, whom we called “responders”; the remainder were “non-responders”. To our surprise, even prior to therapy, responders and non-responders displayed different patterns of brain reaction to bladder filling: at baseline, responders showed activation of dACC and insula (circuit 2 of the working model) while non-responders showed deactivation of the mPFC and elements of circuit 1. After treatment, dACC activation tended to decrease among

responders and some of them may have begun to use circuit 1; by contrast, there was no change in brain activity among non-responders.

This approach thus confirmed that dACC and mPFC were key but left unanswered questions: Are there phenotypes of UI that respond differently to therapy? Do white-matter structural abnormalities cause or contribute to UI? If so, are they responsible for the existence of phenotypes? Our aim was to address these questions by secondary analysis of data gathered during the BFB trial, using methods that were new to this field: diffusion tensor imaging (DTI) and voxel-based morphometry (VBM). We also tried to replicate in a new cohort the WMH results reported previously.^{8,14}

Materials and Methods

We analyzed data from subjects who completed a trial of BFB for UI.¹⁸ All were community-dwelling, mobile, and cognitively intact older women with UI, recruited by newspaper advertisements. Each completed a three-day voiding diary and underwent detailed clinical and videourodynamic evaluation. All underwent functional brain imaging (3T-fMRI) while fluid was being instilled and withdrawn from the bladder following a standardized protocol;¹⁸ they also had structural MRI scans designed to detect white-matter hyperintensities, impaired white-matter integrity, and local atrophy or hypertrophy.

Eligibility included age ≥ 60 years, urgency-predominant incontinence with ≥ 5 UI episodes/week for ≥ 3 months by history, and ≥ 1 episode on the bladder diary. We excluded subjects with any clinically apparent neurological lesion or failure to demonstrate detrusor overactivity (DO) on urodynamics. Subjects taking anticholinergic agents chronically were eligible if the dose was unchanged before and during the study. Continent controls in the same age range were recruited with similar inclusion and exclusion criteria, except that they had to have no UI by self-report or bladder diary and no DO on urodynamics or in the scanner. Subjects gave written informed consent and all studies were approved by the University of Pittsburgh IRB.

We attempted to replicate previous WMH results^{8,14} and extend them through use of *diffusion tensor imaging* (DTI).²⁰ DTI maps fractional anisotropy (FA), and can detect impaired white-matter integrity that is not apparent as WMH. We also used *voxel-based morphometry* (VBM)²¹ to identify local atrophy or hypertrophy of gray matter.

Technical details are provided in the supporting material.

Results

For most analyses, data were available for 11 continent controls and 60 subjects with UI (27 responders and 33 non-responders) (Table 1). For VBM however, there were 10 continent controls. Despite identical inclusion criteria, UI subjects were a little older than controls and non-responders were slightly older than responders. Since WMH increase with age,⁷ results were age-adjusted where appropriate. All subjects were mobile and cognitively intact, with no significant differences in MMSE or TRAILS scores between patients and controls, or between responders and non-responders. Trails A & B (obtained in 45 UIs)

test executive function and were close to normal for age.²² A history of past depression was found among more patients (28%) than controls (18%), a non-significant difference. Eight patients (13%) continued to take a stable dose of anticholinergic medication during the trial, unlike our previous study.³ Baseline UUI frequency was similar in responders and non-responders. There were unremarkable differences between urodynamic parameters representing desire to void and bladder capacity. Involuntary detrusor contraction (DO) amplitude and DO velocity (rate of change of detrusor pressure during DO contraction) appeared smaller than in the previous study³ and DO velocity no longer correlated with improvement in UUI. These changes may reflect smaller sample size or a different patient population.

Structural MRI: White Matter Hyperintensities

Because the WMH data (Tables 2 and 3) were skewed, we used logarithmic transformation to improve normality and enable use of general linear modeling and ANOVA, as in the supplementary tables.

UUI Subjects vs. Controls: We first performed univariate ANOVA for the logarithmically-transformed global WMH volume at baseline, with age and group (normal/UUI) as covariates. The contrast normal vs UUI was significant ($P=0.039$) (Supplementary Table 1). Age did not quite contribute significantly to the variance ($P=0.096$). With similar ANOVAs we generated age-adjusted P-values for each of 19 white-matter tracts, as shown in Table 2, left panel. The burden of WMH was significantly greater in UUI patients than in controls, not only globally but also in two specific tracts which had been observed previously:¹⁴ the superior longitudinal fasciculus (SLFB) and the left upper cingulum (CgUL).

Responders vs. Non-Responders: The unadjusted WMH burden appeared to differ between responders and non-responders (Table 2, right panel), but to allow for possible confounding by age we performed a univariate ANOVA for log-transformed global WMH burden at baseline, with age and response status as covariates (Supplementary Table 3). Similar ANOVAs were performed in 19 tracts. WMH values tended to differ between responders and non-responders, not only globally ($P=0.06$), but also in SLFTL ($P<0.05$) and right and left ATR ($P=0.07$) (also identified in a previous study).¹⁴ At baseline, WMH burden tended to be greater in responders than in non-responders (16/19 tracts), implying predictive behavior.

Pre-BFB vs post-BFB: The unadjusted data (Table 3) suggested that WMH increases after treatment among nonresponders and declines somewhat among responders – potentially mediative behavior. We therefore performed, globally and in the tracts, a repeated-measures GLM of WMH (logarithmically transformed) with age and responder-nonresponder status as independent variables (Supplementary Table 3). This confirmed the significance of the interaction [pre/post * resp/nonresp; *significant p-value suggests a significant difference between the pre/post change in responders and the pre/post change in non-responders*] both globally and in ATRR ($P=0.013$) (Table 3). The pre/post changes in WMH did not depend on age (Supplementary Table 3).

Structural MRI: Diffusion Tensor Imaging (DTI)

UII Patients vs. Controls: White-matter integrity (as assessed by fractional anisotropy [FA]) did not differ significantly between those with UII and controls, when judged at cluster level with correction for multiple comparisons. Without this correction, however, white matter integrity (FA) was reduced in a long tract identified by the Johns Hopkins atlas²³ as part of the left cingulum (see Fig. 2). The cingulum connects the entorhinal cortex with midcingulate and parahippocampal regions²⁴ probably involved in bladder control.^{10,18}

Responders vs. Non-Responders: No baseline differences were seen on DTI between responders and non-responders to BFB, with or without correction for multiple comparisons (data not shown).

Pre-BFB vs post-BFB: There were no significant changes from pre- to post BFB, except in responders, in a few voxels in a left brainstem/cerebellar peduncle region.

Structural MRI: Voxel Based Morphometry (VBM)

UII Patients vs. Controls: Postulating that the cingulum pathway is degraded in UII (Fig. 2), we expected its neural traffic to be reduced, with consequent atrophy of gray matter at the termini, including the parahippocampal region. Indeed, VBM showed more severe hippocampal and parahippocampal atrophy in subjects with UII than in controls at baseline (Fig. 3A). Results were unchanged when we excluded the 8 subjects on an anticholinergic.

Responders vs. Non-Responders: Compared with non-responders at baseline, responders had *increased* tissue volume (hypertrophy) in the midcingulate (dACC); see Fig. 3B.

Pre-BFB vs post-BFB: There were no significant changes post-BFB in the parahippocampal region. Paired t-tests showed a non-significant trend to reduction in tissue volume in parietal and frontal lobes, in responders but not in non-responders.

Discussion

In older community-dwelling women, the presence of urgency incontinence (UII) is associated with damage to white-matter pathways both globally and in a few specific tracts, confirming what has previously been reported,^{7,18,25} and suggesting that white-matter damage may contribute causally to UII. These tracts include the superior longitudinal fasciculus (SLF) and, notably, the upper left cingulum (CgUL, Table 2), despite the relatively small size and limited amount of white matter in the cingulate tracts. Moreover the suggestion from diffusion tensor imaging (DTI) that left cingulate damage is associated with the presence of UII (Fig. 2) tends to support this chain of causation. While this reflects results uncorrected for multiple comparisons, we are inclined to comment on it since the entire tract of multiple contiguous voxels shows a significant difference in a biologically plausible location. Furthermore, the cingulum may be part of the white-matter pathway, circuit 1 of the working model (Fig. 1), that enables the ventromedial prefrontal cortex to inhibit voiding and thus attempt to maintain continence. The cingulum also projects to the

gray matter in parahippocampal regions²⁴ involved in bladder control,^{10,18} forming circuit 3 of the model. Therefore we expect that damage to the cingulum should reduce neural traffic and lead to parahippocampal atrophy, an expectation confirmed by voxel-based morphometry (Fig. 3A).

Thus, compared with age-adjusted controls, UUI in older women is associated with an increase in damage to CNS white matter, in both responders and non-responders, both globally and in specific tracts, as well as gray-matter atrophy near the terminus of one of the damaged white matter tracts. The association is present whether the damage was overt and easily recognized as WMH on MRI or whether it was detectable only by DTI.

Although baseline WMH damage was more severe among responders than among non-responders (Table 3) an improvement in WMH did not mediate response of UUI to BFB since improvement in WMH was not observed among those who responded. The slight changes observed in the opposite direction among non-responders may be simply a reaction to another abnormality or an epiphenomenon. Summarizing, low baseline WMH *predicted* nonresponse to subsequent BFB, and BFB was associated with increased WMH in nonresponders but not in responders. While it is possible that increased WMH burden might mediate UUI compared to continent controls, the WMH change seen in nonresponders after therapy cannot logically *mediate* the clinical improvement seen in responders; it is either a reaction to another abnormality or an epiphenomenon.

These WMH data are consistent with our working model and with previous reports and reviews^{7,8} that have found an association between UUI and white-matter hyperintensities. They also suggest that BFB works best among UUI patients in whom WMH damage is more severe. In such patients, this type of damage may play a disproportionate role in UUI. Thus an intervention such as BFB, targeted at the brain, may facilitate development of compensatory brain mechanisms or “work-arounds,” whereas among patients whose UUI occurs in the setting of satisfactory brain function, a therapy like BFB that targets the brain might have much less of an impact. Most importantly, the abnormalities predictive of response do not mediate that response but are either a reaction to another abnormality or simply epiphenomena. Thus in answer to the question posed in the title, brain structural abnormalities do – to an extent – differentiate separate forms of urgency urinary incontinence, and the distinction may help identify UUI patients more responsive to BFB.

One other finding supports the working model (Fig. 1):¹⁰ VBM showed midcingulate *hypertrophy* in responders relative to non-responders (Fig. 3B). Such hypertrophy is consistent with the observation¹⁴ that responders react to a full bladder and urgency with strong midcingulate activation, while non-responders do not, thus facilitating a kind of midcingulate “exercise hypertrophy” in responders.

Limitations: Only women were enrolled (to avoid confounding by the effects of the prostate). The small size of the continent control group reflects the difficulty of recruiting symptom-free older women and the stringency of the inclusion/exclusion criteria; the latter is also a strength of the study. Similarly the incontinent subjects were stringently selected to exhibit both the signs and the symptoms of UUI. Clinically, most patients exhibit less clear-

cut behavior, but for a mechanistic study it seemed preferable to choose homogeneous and well-defined groups. Further, the study has the disadvantages inherent in any secondary approach: it is based on measurements that cannot now be changed or repeated and may have limited statistical power for new sub-analyses.

Conclusions

UUI is common in older women but remains in many cases poorly understood and suboptimally treated. Combined with our previous data,¹⁸ the present study suggests that there may be two general types, or phenotypes, of UUI: one in which brain abnormalities play the predominant role and thus are best addressed by brain targeted therapy such as BFB, and one in which abnormalities of these key brain centers are less pronounced and suggest that the predominant cause does not involve these centers; in such patients, therapy targeting the bladder or brain centers hitherto unidentified may be more appropriate. We are not suggesting that neuroimaging be used clinically, however, because of its still limited accuracy for individuals, high cost, and limited access. Instead, our hope is that these data will help to advance understanding of UUI and thereby lead to better therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

Working model, showing 3 putative neural circuits that control the voiding reflex by inhibiting the periaqueductal gray (PAG). PMC = pontine micturition center, Sa = sacral parasympathetic region, ON = nucleus of Onuf, th = thalamus, IPFC and mPFC = lateral and medial prefrontal cortex, respectively, dACC/SMA = dorsal anterior cingulate cortex and supplementary motor area.

Fig. 2.

Results of tract-based spatial statistics (TBSS), applied to diffusion tensor imaging (DTI) in continent and urgency-incontinent women. The figure shows a sagittal section at $x = -7$. Green coloring shows skeletonized white-matter tracts for whole group of women with UUI. Red color shows where mean fractional anisotropy (FA) is significantly smaller in UUI than in continent controls ($P < 0.05$ at cluster level, uncorrected for multiple comparisons). The red tract is in the cingulum. An earlier provisional analysis²⁶ identified the adjacent fornix instead, an inconsistency that presumably reflected low statistical power.

Fig. 3.A.
(left). Results of VBM analyses at baseline. Regions where tissue volume was smaller in UUI than in normal controls (atrophy). Blue: significant at $P < 0.05$ at cluster level. Crosshairs are at MNI coordinates $[-29, -16, -28]$. Note that removing those on anticholinergic medications from the analysis did not make any difference to these results.

Fig. 3. B.

(right) Results of VBM analyses at baseline. Regions where tissue volume was larger in responders than in non-responders (relative hypertrophy). Red/yellow: significant at $P < 0.05$ at cluster level. Crosshairs are at [1, 4, 40]. Note that removing those on anticholinergic medications from the analysis did not make any difference to these results.

Table 1.

Selected clinical and urodynamic data (mean $\pm$ SD), for whole UII group, responders and non-responders to BFB, and normal controls, with the significance of differences between them. Variables shown in this table were measured at baseline. Of subjects reporting a stroke, none reported a recent event, none had current neurological deficits, and only 3 had a visible infarct on MRI, which was small in each. Locations were left parietal in one subject, right parietal in another, and bilateral parietal in the third.

	Whole UII group (n=60)	Responders (n=27)	Non-responders (n=33)	Controls (n=11)
Demographic variables				
Age (y)	71.3 $\pm$ 8.5	68.2 $\pm$ 6.7	73.8 $\pm$ 9.1 ^{\$}	64.0 $\pm$ 5.6 [¶]
MMSE /30	29.6 $\pm$ 0.9	29.8 $\pm$ 0.5	29.4 $\pm$ 1.1	29.0 $\pm$ 1.8
Trails A (s)	38 $\pm$ 11	38 $\pm$ 13	37 $\pm$ 10	43 $\pm$ 26
Trails B (s)	93 $\pm$ 43	90 $\pm$ 36	96 $\pm$ 49	82 $\pm$ 35
Depression (Hx)	17 (28%)	6 (22%)	11 (33%)	2 (18%)
Anticholinergic (current use)	8 (13%)	1 (4%)	7 (21%) ^b	0
Diabetes	14 (23%)	5 (19%)	9 (27%)	0
Stroke	9 (15%)	4 (15%)	5 (15%)	1 (9%)
Hysterectomy	32 (53%)	15 (55%)	17 (51%)	3 (27%)
UII frequency/24h	3.5 $\pm$ 2.3	3.6 $\pm$ 2.5	3.6 $\pm$ 2.2	-
Urodynamic variables				
Maximum cystometric capacity	568 (167)	501	616 (216) [←]	550 (193)
First desire to void (ml)	254 (133)	222 (124)	269 (139)	361 (226) [→]
Strong desire to void (ml)	366 (161)	341 (130)	391 (189)	506 (190) [→]
Detrusor overactivity parameters				
DO amplitude (cmH ₂ O)	13.6 (14.2)	11.6 (10.3)	16.3 (16.8)	-
DO velocity (cmH ₂ O/s)	1.8 (1.7)	1.8 (1.7)	1.7 (1.3)	-

^{\$} = significant responder/nonresponder age difference at 2-tailed heteroscedastic P < 0.01.

[¶] = significant age difference between all UIIs and normal controls at P < 0.01.

^b = significant difference between responders and nonresponders in anticholinergic use (P = 0.047 2-tailed).

[←] = maximum cystometric capacity higher in non-responders than responders

[→] = first desire and strong desire to void both higher in controls than UIIs.

Table 2.

Mean WMH volume at baseline, expressed as a percentage of total brain tissue volume, in whole brain and in 19 tracts identified by the Johns Hopkins brain atlas. P-values show (left panel) age-adjusted significance of the difference between UII subjects and normal controls, using ANOVAs in Supplementary Table 1; and (right panel) between non-responders and responders to BFB using age-adjusted ANOVA, as in Supplementary Table 2. WMH burden in tract CgLR is too small to analyze.

WM Tract	Mean normalized WMH volume %		P-value age-adjusted	Mean normalized WMH volume %		P-value age-adjusted
	UIIs	Controls	UIIs - controls	Resp	Non-resp	Resp - nonresp
Whole brain	0.2064	0.0698	0.04 *	0.2417	0.1776	0.06
ATRL	0.0316	0.0180	0.5	0.0382	0.0261	0.07
ATRR	0.0556	0.0313	0.7	0.0662	0.0469	0.07
CCF	0.0305	0.0158	0.8	0.0379	0.0244	0.1
CCO	0.0319	0.0095	0.7	0.0449	0.0213	0.4
CSTL	0.0043	0.0002	0.7	0.0034	0.0051	0.1
CSTR	0.0054	0.0003	0.4	0.0074	0.0038	0.3
CgLL	0.0002	0.0002	0.3	0.0003	0.0002	0.3
CgLR	-	-	-	-	-	-
CgUL	0.0048	0.0000	0.01 *	0.0063	0.0036	0.6
CgUR	0.0032	0.0038	0.3	0.0019	0.0043	0.1
IFOL	0.0253	0.0080	0.4	0.0341	0.0182	0.15
IFOR	0.0550	0.0152	0.4	0.0593	0.0459	0.3
ILFL	0.0132	0.0015	0.3	0.0143	0.0123	0.6
ILFR	0.0048	0.0011	0.5	0.0069	0.0032	0.2
SLFBL	0.0186	0.0005	0.05 *	0.0146	0.0219	0.15
SLFBR	0.0155	0.0021	0.3	0.0163	0.0148	0.2
SLFTL	0.0117	0.0004	0.8	0.0080	0.0147	0.3
SLFTR	0.0073	0.0000	0.3	0.0092	0.0058	0.05 *
UNCL	0.0088	0.0036	0.2	0.0124	0.0059	0.2
UNCR	0.0132	0.0068	0.7	0.0148	0.0118	0.2

* = significant at $P < 0.05$.

Keys: ATRL/R = anterior thalamic radiation (left or right), CCF/O = corpus callosum (frontal or occipital), CSTL/R = corticospinal tract (left or right), CgLL/R = cingulate (lower part left or right), CgUL/R = cingulate (upper part left or right), IFOL/R = inferior fronto-occipital fasciculus (left or right), ILFL/R = inferior longitudinal fasciculus (left or right), SLFBL/R = entire superior longitudinal fasciculus (left or right), SLFTL/R = superior longitudinal fasciculus (the branch to the temporal lobe, left or right), UNCL/R = uncinate fasciculus (left or right).

Table 3,

Mean WMH volume at baseline and post-BFB in responders and nonresponders, expressed as a percentage of total brain tissue volume, in whole brain and in 20 tracts. P-values show significance of the interaction [pre-post * response] obtained from repeated-measures GLM in Supplementary Table 3.

WM Tract	Mean normalized WMH volume % responders		Mean normalized WMH volume % nonresponders		P-value of interaction pre/post * resp/nonresp
	Pre-BFB	Post-BFB	Pre-BFB	Post-BFB	
Whole brain	0.2416	0.2279	0.1776	0.2036	0.04 *
ATRL	0.0383	0.0343	0.0261	0.0311	0.08
ATRR	0.0662	0.0636	0.0469	0.0582	0.013 *
CCF	0.0378	0.0393	0.0244	0.0283	0.6
CCO	0.0449	0.0396	0.0213	0.0245	0.19
CSTL	0.0033	0.0056	0.0051	0.0053	0.8
CSTR	0.0074	0.0083	0.0038	0.0042	0.9
CgLL	0.0003	0.0004	0.0001	0.0001	0.28
CgLR	0	0.0002	0	0.0000	-
CgUL	0.0063	0.0045	0.0036	0.0000	0.9
CgUR	0.0019	0.0001	0.0042	0.0045	0.7
IFOL	0.0341	0.0335	0.0181	0.0224	0.05
IFOR	0.0593	0.0533	0.0460	0.0521	0.11
ILFL	0.0143	0.0143	0.0123	0.0151	0.6
ILFR	0.0068	0.0048	0.0032	0.0036	0.17
SLFBL	0.0146	0.0139	0.0219	0.0235	0.19
SLFBR	0.0163	0.0164	0.0148	0.0166	0.12
SLFTL	0.0086	0.0077	0.0147	0.0149	0.6
SLFTR	0.0073	0.0077	0.0058	0.0059	0.17
UNCL	0.0124	0.0106	0.0059	0.0077	0.13
UNCR	0.0148	0.0148	0.0118	0.0144	0.22

* = significant at $P < 0.05$.

Keys: ATRL/R = anterior thalamic radiation (left or right), CCF/O = corpus callosum (frontal or occipital), CSTL/R = corticospinal tract (left or right), CgLL/R = cingulate (lower part left or right), CgUL/R = cingulate (upper part left or right), IFOL/R = inferior fronto-occipital fasciculus (left or right), ILFL/R = inferior longitudinal fasciculus (left or right), SLFBL/R = entire superior longitudinal fasciculus (left or right), SLFTL/R = superior longitudinal fasciculus (the branch to the temporal lobe, left or right), UNCL/R = uncinate fasciculus (left or right).