Comparison of Automated Brain Segmentation Tools in FTD: Implications for Imaging Biomarker Choice in Clinical Trials

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BACKGROUND

Automated measures of volumetric brain loss are valuable markers of disease progression and commonly used as endpoints in neurodegenerative therapeutic trials. However validation of these techniques within the FTD patient population is currently lacking.

METHODS

We compared six widely used automated segmentation tools to extract whole brain volumes: BMAPS[1], SPM12[2], GIF[3], Freesurfer (6.0)[4], MALPEM (v1.2)[5] and SIENAX[6] in 264 individuals who had undergone 2 same-scanner 3DT1 magnetic resonance imaging (MRI). Minimal MRI interval for inclusion was 6 months (**Table 1**). All techniques were applied using standard published pipelines and in native space, except SIENAX which was applied to images after transformation into MNI125 space (**Figure 1**). For techniques that produced multi-label or multi-tissue type parcellations, all relevant regions were summed to produce a single whole brain volume. Annualised rates of change were calculated by subtraction of raw segmented volumes, or application of the boundary shift integral (BSI) in both kn-means (knBSI) and generalised (gBSI) forms. The longitudinal pipelines for VBM and SIENA were also applied to derive annual percentage brain volume change (PBVC).

Cohorts		Clinical					Genetic			Pathological	
	Controls	bvFTD	svPPA	nfvPPA	PPA-NOS	lvPPA	*MAPT*	*C9orf72*	*GRN*	Tau	TDP-43
N	79	66	45	46	7	21	16	10	8	19	33
M:F	35:45	50:16	24:21	26:20	4:3	15:6	9:7	9:1	3:5	12:7	20:13
Age at baseline	62.4 (11.6)	62.6 (8.6)	63.7 (7.8)	66.0 (7.5)	62.6 (7.0)	67.4 (7.4)	55.4 (7.2)	62.5 (6.0)	61.2 (7.2)	56.2 (7.2)	62.8 (6.1)
Age at onset	NA	56.7 (8.8)	59.0 (7.5)	61.6 (7.4)	60.1 (7.5)	63.3 (7.1)	49.1 (5.8)	55.6 (8.6)	58.0 (6.4)	50.7 (7.0)	58.0 (7.1)
Disease duration	NA	5.9 (3.9)	4.7 (1.9)	4.4 (1.9)	2.4 (1.4)	4.1 (1.9)	6.3 (3.9)	6.9 (4.4)	3.2 (3.4)	5.6 (3.7)	4.8 (3.5)
Scan interval	1.6 (0.8)	1.4 (0.8)	1.5 (0.8)	1.3 (0.6)	1.6 (0.7)	1.3 (0.7)	1.9 (1.2)	1.0 (0.4)	1.2 (0.4)	1.8 (1.2)	1.5 (0.9)

Table 1: Patient demographics for all FTD subgroups and healthy controls. Figures are in years for bottom four rows.

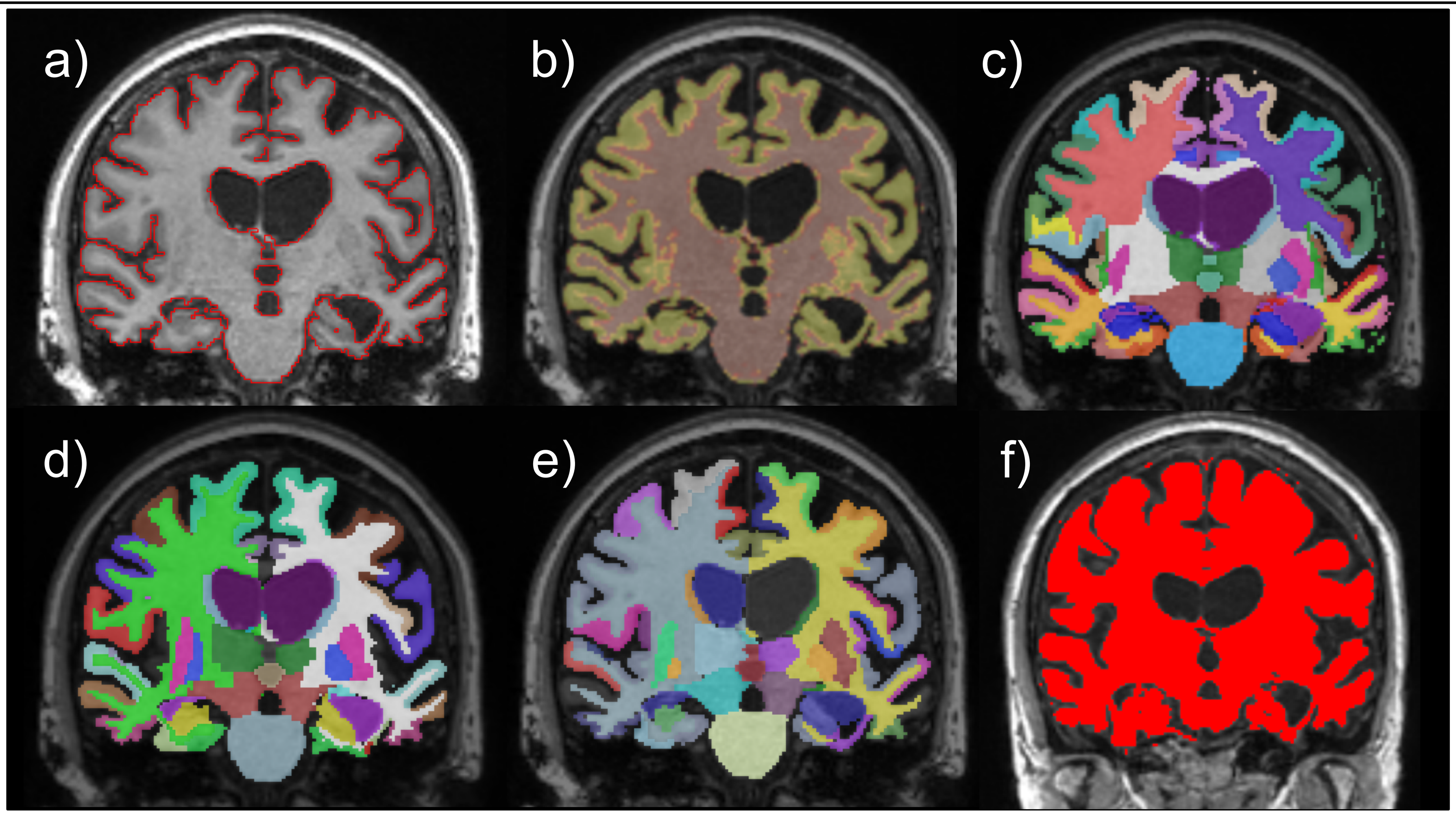

Figure 1: Representative slice from the same patient for a) BMAPS b) SPM12 c) GIF d) Freesurfer e) MALPEM f) SIENAX.

RESULTS

Annual rates of change (**Table 2**) are expressed as percentage loss from baseline volume (mean (standard deviation)). All analyses were performed in STATA 14. Effect sizes with 95% confidence intervals (CI) were calculated using bootstrapping (2000 replications) and applied to all annual rates of change, comparing controls to each of the patient subgroups for all techniques. Sample size calculations to detect a 25% treatment effect with 80% power were derived based on these effect size analyses (**Table 3**). Key findings: There were clear qualitative and quantitative differences between techniques with BMAPS, GIF and SPM most often performing best in accurately segmenting the whole brain structures and producing the lowest sample sizes. Raw segmented brain volume difference was overall a poor biomarker with substantial improvements gained once either BSI technique was applied. Subgroups with more homogeneous rates of atrophy (PPA groups clinically, *MAPT* and *GRN* genetically, tauopathies pathologically) tended to have lower sample sizes.

Technique Annualised change (%bl)			Clinical					Genetic			Pathology	
		Controls	bvFTD	svPPA	nfvPPA	PPA-NOS	lvPPA	*MAPT*	*C9orf72*	*GRN*	Tau	TDP-43
BMAPS	raw volumes	0.5 (0.9)	2.0 (1.8)	2.4 (1.2)	2.8 (1.9)	2.8 (1.0)	2.5 (1.6)	1.8 (1.4)	2.2 (1.5)	3.0 (2.6)	2.0 (1.3)	2.6 (1.7)
	knBSI	0.5 (0.8)	1.8 (1.3)	2.2 (0.9)	2.6 (1.4)	2.6 (0.9)	2.3 (1.0)	1.8 (1.0)	2.0 (1.3)	3.7 (1.8)	1.9 (1.0)	2.5 (1.3)
MALPEM	raw volumes	0.0 (1.8)	0.6 (4.3)	0.5 (1.9)	0.8 (1.9)	1.5 (0.7)	0.9 (4.4)	0.5 (1.0)	0.7 (1.6)	0.0 (4.2)	0.7 (1.1)	0.3 (5.4)
	knBSI	0.3 (0.5)	1.0 (0.7)	1.2 (0.6)	1.4 (0.9)	1.5 (0.5)	1.0 (0.8)	1.0 (0.7)	0.9 (0.5)	2.1 (0.9)	1.1 (0.7)	1.3 (0.7)
	gBSI	0.4 (0.7)	1.6 (1.1)	1.8 (0.7)	2.0 (1.1)	2.3 (0.7)	1.7 (1.2)	1.5 (0.8)	1.3 (0.9)	3.1 (1.3)	1.5 (0.9)	2.0 (1.1)
SIENAX	raw volumes	0.4 (1.0)	2.3 (9.6)	1.4 (2.4)	1.0 (5.7)	2.4 (1.1)	1.7 (1.6)	0.8 (2.9)	1.3 (1.5)	1.5 (1.9)	1.0 (2.7)	1.5 (1.7)
	knBSI	0.5 (0.7)	1.6 (1.2)	1.9 (0.8)	2.4 (1.3)	2.6 (0.8)	1.9 (1.4)	1.6 (1.0)	1.7 (1.2)	3.2 (1.6)	1.7 (1.0)	2.2 (1.2)
Freesurfer	raw volumes	0.7 (1.3)	2.3 (3.9)	2.0 (4.1)	2.5 (3.1)	2.7 (0.9)	0.8 (3.6)	1.3 (1.8)	2.5 (1.7)	3.7 (1.7)	1.8 (2.3)	2.9 (3.2)
	knBSI	0.3 (0.6)	1.6 (1.3)	1.9 (0.9)	2.4 (1.3)	2.5 (0.8)	1.8 (1.4)	1.7 (1.0)	1.6 (1.2)	2.6 (2.1)	1.8 (1.0)	2.1 (1.4)
GIF	raw volumes	0.2 (0.6)	1.1 (1.2)	1.1 (0.7)	1.4 (0.8)	1.7 (0.8)	1.2 (1.7)	1.0 (0.6)	1.4 (1.0)	1.2 (1.8)	1.1 (0.6)	1.3 (1.1)
	knBSI	0.5 (0.7)	1.7 (1.2)	1.9 (0.8)	2.1 (1.1)	2.4 (0.8)	1.9 (1.2)	1.6 (0.8)	1.6 (1.1)	3.1 (1.4)	1.6 (0.8)	2.2 (1.1)
	gBSI	0.3 (0.6)	1.7 (1.2)	1.9 (0.7)	2.3 (1.1)	2.4 (0.8)	2.0 (0.8)	1.7 (0.8)	1.5 (1.1)	3.5 (1.5)	1.7 (0.8)	2.1 (1.2)
SPM	raw volumes	0.6 (1.0)	2.8 (2.4)	3.7 (4.2)	3.2 (2.3)	3.3 (1.0)	3.6 (2.7)	2.1 (1.7)	2.6 (3.0)	4.2 (3.7)	2.4 (1.6)	3.2 (2.5)
	knBSI	0.5 (0.6)	1.9 (1.5)	2.1 (1.0)	2.6 (1.5)	2.7 (1.0)	2.2 (1.4)	1.8 (1.0)	1.7 (1.5)	3.7 (2.0)	1.9 (1.0)	2.5 (1.5)
	gBSI	0.5 (0.8)	2.1 (1.6)	2.4 (0.9)	2.8 (1.5)	2.8 (0.8)	2.3 (1.5)	2.0 (1.1)	1.7 (1.3)	3.9 (2.1)	2.1 (1.1)	2.6 (1.6)
SIENA	PBVC	0.6 (0.7)	2.4 (1.9)	3.0 (1.0)	3.3 (2.0)	3.2 (1.2)	3.0 (1.3)	2.2 (1.2)	2.2 (1.1)	4.4 (2.4)	2.4 (1.2)	2.9 (1.8)
Long VBM	PBVC	0.2 (0.6)	1.0 (0.9)	1.0 (0.7)	1.2 (1.0)	1.6 (0.6)	1.5 (0.7)	1.0 (0.9)	1.2 (0.8)	0.6 (1.2)	1.0 (0.8)	0.9 (0.9)

Table 2: Mean (standard deviation) annual rates of atrophy as a percentage loss from baseline volume.

Technique sample size [95% CI]		Clinical					Genetic			Pathology	
		bvFTD	svPPA	nfvPPA	PPA-NOS	lvPPA	*MAPT*	*C9orf72*	*GRN*	Tau	TDP-43
BMAPS	raw volumes	151 [95, 290]	83 [49, 158]	74 [40, 169]	42 [2, 91]	103 [44, 260]	75 [40, 178]	166 [71, 619]	130 [15, 48882]	70 [38, 156]	92 [46, 202]
	knBSI	152 [96, 285]	51 [30, 106]	81 [42, 189]	41 [16, 72]	48 [23, 117]	69 [30, 151]	164 [62, 707]	71 [16, 461]	71 [36, 157]	87 [49, 179]
MALPEM	raw volumes	108663 [NA, ∞]	47513 [NA/∞]	3809 [389, 4610]	50 [16, 226]	7528470 [NA/∞]	4567 [NA/∞]	2925 [NA/∞]	111505 [NA/∞]	1597 [248, 2628]	28499 [NA/∞]
	knBSI	151 [89, 291]	54 [32, 106]	82 [40, 216]	41 [9, 200]	330 [48, 52563]	127 [49, 503]	131 [46, 501]	58 [27, 139]	129 [57, 375]	83 [45, 189]
	gBSI	140 [91,237]	47 [29, 96]	80 [40, 187]	39 [17,95]	219 [33, 76750]	86 [35, 268]	167 [77, 441]	54 [11, 287]	90 [43, 238]	90 [54, 172]
SIENAX	raw volumes	1374 [358, 1703766]	364 [185, 1005]	374 [139, 4203]	65 [16, 312]	347 [101, 11464]	8883 [NA/∞]	568 [115, 2487]	375 [NA/∞]	4348 [NA/∞]	413 [189, 1937]
	knBSI	220 [135, 453]	57 [33, 133]	83 [44, 199]	35 [12, 85]	277 [42, 910415]	95 [51, 207]	194 [71, 1073]	85 [16, 776]	103 [60, 206]	122 [68, 248]
Freesurfer	raw volumes	634 [287, 11310]	3782 [368, 5196]	352 [181, 1889]	46 [11, 210]	13793 [NA/∞]	306 [72, 9669]	149 [60, 1036]	110 [48, 274]	242 [67, 1806313]	501 [213, 3683]
	knBSI	158 [101, 284]	77 [46, 160]	86 [50, 182]	35 [18, 68]	207 [36, 11046]	68 [29, 154]	200 [82, 1018]	125 [14, 11037]	69 [35, 144]	142 [77, 293]
GIF	raw volumes	306 [170, 736]	109 [49, 430]	101 [47, 406]	70 [28, 210]	512 [58, 13665]	69 [35, 190]	180 [46, 1116]	291 [25, 403]	57 [30, 139]	154 [72, 496]
	knBSI	164 [101, 316]	48 [30, 94]	83 [42, 192]	43 [17, 84]	212 [30, 26350]	65 [27, 136]	198 [72, 1131]	63 [13, 397]	67 [33, 138]	95 [53, 194]
	gBSI	149 [91, 279]	47 [29, 100]	75 [39, 167]	42 [17, 78]	39 [20, 83]	59 [27, 115]	193 [72, 1049]	63 [11, 435]	60 [32, 117]	91 [51, 190]
SPM	raw volumes	190 [118, 355]	67 [38, 130]	158 [83, 467]	38 [16, 113]	248 [67, 75516]	86 [39, 313]	672 [180, 8653506]	85 [37, 224]	71 [33, 261]	153 [76, 437]
	knBSI	193 [128, 342]	57 [33, 116]	91 [48, 209]	52 [22, 84]	198 [36, 33512]	83 [42, 178]	293 [115, 2118]	68 [14, 390]	82 [45, 171]	110 [63, 216]
	gBSI	165 [108, 283]	43 [26, 88]	72 [37, 159]	34 [15, 60]	204 [37, 73559]	66 [30, 150]	219 [90, 811]	64 [16, 346]	69 [33, 146]	94 [53, 181]
SIENA	PBVC	186 [119, 326]	35 [24, 56]	83 [50, 165]	55 [26, 94]	44 [23, 118]	80 [30, 383]	99 [36, 394]	90 [24, 671]	74 [31, 297]	126 [68, 279]
Long_VPM	PBVC	175 [107, 327]	207 [94, 1016]	248 [102, 2430]	51 [26, 137]	60 [28, 179]	158 [59, 915]	174 [61, 849]	5618 [NA/∞]	143 [NA/∞]	356 [NA/∞]

Table 3: Sample size estimates per treatment arm to detect a 25% reduction in volume loss at 80% power with 95% confidence intervals in parentheses.

CONCLUSIONS

Automated whole brain segmentation techniques are applicable across the full FTD spectrum. However performance qualitatively and quantitatively varies, so careful selection of tools will be important in upcoming FTD therapeutic trials. Application of the BSI substantially improves the variability of measures of volume loss and should be used preferentially to raw volume change as an imaging biomarker. Enrolment targeting more stratified and homogeneous groups will also prove helpful in lowering sample sizes required.

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