Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Detailed Information on MRI Scan and Preprocessing of MRI Data in FreeSurfer

High-resolution T1-weighted images were acquired using a three-dimensional magnetization prepared rapid acquisition gradient echo: 256x256 matrix, repetition time=2250ms, echo time=4.18ms, flip angle=9°, 176 slices, 1mm slice thickness, field of view=25.6x25.6cm, acquisition time=5’14”. Images were visually checked for motion distortion.

Following steps were conducted using FreeSurfer v5.3.0: (1) skull stripping using hybrid watershed/surface deformation[1]; (2) automated transformation to Talairach space; (3) intensity normalization[2]; (4) subject-specific segmentation of subcortical white matter and deep gray matter volumetric structures[3]; and (5) calculation of cortical thickness/volume of ten a-priori selected cortical regions based on the Desikan gyral parcellation[4] (caudal middle frontal, inferior parietal, inferior temporal, medial orbitofrontal, parahippocampal, postcentral, precentral, rostral middle frontal, superior parietal, and supramarginal gyri) and volumes of five a-priori selected regions from the FreeSurfer subcortical segmentation (amygdala, caudate, hippocampus, putamen, and thalamus).[3].

eReferences

1. Segonne F, Dale AM, Busa E, et al. A hybrid approach to the skull stripping problem in MRI. *Neuroimage*. 2004;22(3):1060-1075. doi:10.1016/j.neuroimage.2004.03.032.
2. Sled JG, Zijdenbos AP, Evans AC. A nonparametric method for automatic correction of intensity nonuniformity in MRI data. *IEEE Trans Med Imaging*. 1998;17(1):87-97. doi:10.1109/42.668698.
3. Fischl B, Salat DH, Busa E, et al. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron*. 2002;33(3):341-355.
4. Desikan RS, Ségonne F, Fischl B, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage*. 2006;31(3):968-980. doi:10.1016/j.neuroimage.2006.01.021.

eTable 1. Main Differences Between the Two Treatment Arms

Experimental treatment	Control treatment
Pain Neuroscience Education	Traditional Back/Neck School
Cognition-Targeted, Biopsychosocial Approach	Biomedical Approach
Time-Contingent Exercise Program (“Perform this exercise 10 times regardless the symptoms it might induce.”)	Pain-Contingent Exercise Program (“Stop or adapt the exercise as soon as symptoms occur.”)

eTable 2. Effect of Physiotherapy Treatment on Gray Matter Cortical Thickness and Subcortical Volumes in People With Chronic Spinal Pain (n=120)

		Experimental treatment		**Control treatment**		**Mean group Difference [95% CI]**	**Main effect of Time**	**Interaction effect**	**Bonferroni Post-Hoc tests**	
		Mean±SD	% change rel. to baseline	Mean±SD	% change rel. to baseline					
Left hemisphere cortical thickness (mm)										
Caudal middle frontal	Base	2.661±.017	-	2.618±.017	-	.043 [-.004,.090]	F=17.122 **p<.001**	F=.577 p=.56	Time	12mo<Base,3mo **p=.001 p<.001**[a] **p=.02, p=.01**[b]
	3mo	2.664±.019	+.11%	2.617±.019	-.04%	.047 [-.007, .101]				
	12mo	2.625±.018	-1.46%	2.591±.018	-.99%	.034 [-.016,.083]				
Inferior parietal	Base	2.493±.015	-	2.468±.015	-	.025 [-.018,.068]	F=6.699 **p=.002**	F=.995 p=.37	Time	3mo<Base **p=.02**[a]
	3mo	2.469±.018	-.96%	2.447±.018	-.85%	.021 [-.029,.072]				
	12mo	2.476±.016	+.28%	2.472±.016	+1.02%	.004 [-.041,.048]				
Inferior temporal	Base	2.719±.018	-	2.708±.017	-	.010 [-.039,.060]	F=.387 p=.68	F=1.129 p=.33		
	3mo	2.721±.020	+.07%	2.693±.020	-.55%	.029 [-.029,.086]				
	12mo	2.727±.021	+.22%	2.692±.022	-.04%	.035 [-.025,.095]				
Medial orbito-frontal	Base	2.500±.020	-	2.417±.020	-	.082 [.026,.138]	F=2.126 p=.13	F=2.801 p=.07	Group	Base: **p=.004** 3mo: **p=.02** 12mo: p=.09
	3mo	2.483±.020	-.68%	2.414±.020	-.12%	.069 [.012,.126]				
	12mo	2.467±.019	-.64%	2.420±.019	+.25%	.047 [-.007,.101]				

Parahippo-campal	Base	2.804±.035	-	2.807±.035	-	-.004 [-.103,.095]				
	3mo	2.801±.038	-.11%	2.803±.038	-.14%	-.002 [-.109,.105]	F=.746 p=.48	F=.012 p=.99		
	12mo	2.794±.037	-.25%	2.798±.037	-.18%	-.004 [-.107,.099]				
Postcentral	Base	2.214±.015	-	2.192±.015	-	.022 [-.020,.064]				
	3mo	2.210±.016	-.18%	2.186±.016	-.27%	.024 [-.021,.069]	F=2.149 p=.12	F=.090 p=.91		
	12mo	2.207±.016	-.14%	2.180±.015	-.27%	.026 [-.019,.071]				
Precentral	Base	2.713±.017	-	2.674±.017	-	.039 [-.009,.086]				
	3mo	2.710±.018	-.11%	2.673±.018	-.04%	.037 [-.014,.089]	F=1.381 p=.26	F=.165 p=.85		
	12mo	2.707±.017	-.11%	2.663±.017	-.37%	.043 [-.004,.090]				
Rostral middle frontal	Base	2.458±.016	-	2.436±.016	-	.022 [-.024,.067]			Time	12mo<3mo **p=.008**[a] 12mo<Base,3mo **p=.04**, **p=.004**[b]
	3mo	2.467±.017	+.37%	2.444±.017	+.33%	.023 [-.026,.071]	F=10.545 **p<.001**	F=.063 p=.94		
	12mo	2.437±.017	-1.22%	2.411±.017	-1.35%	.026 [-.022,.075]				
Superior parietal	Base	2.298±.014	-	2.275±.014	-	.024 [-.015,.063]			Time	NS
	3mo	2.284±.016	-.61%	2.260±.016	-.66%	.024 [-.019,.068]	F=3.976 **p=.02**	F=.822 p=.44		
	12mo	2.283±.014	-.04%	2.272±.014	+.53%	.011 [-.029,.052]				
Supra-marginal	Base	2.634±.015	-	2.622±.015	-	.012 [-.030,.054]				
	3mo	2.627±.017	-.27%	2.616±.017	-.23%	.011 [-.036,.058]	F=1.435 p=.24	F=.039 p=.96		
	12mo	2.628±.015	+.04%	2.614±.015	-.08%	.014				

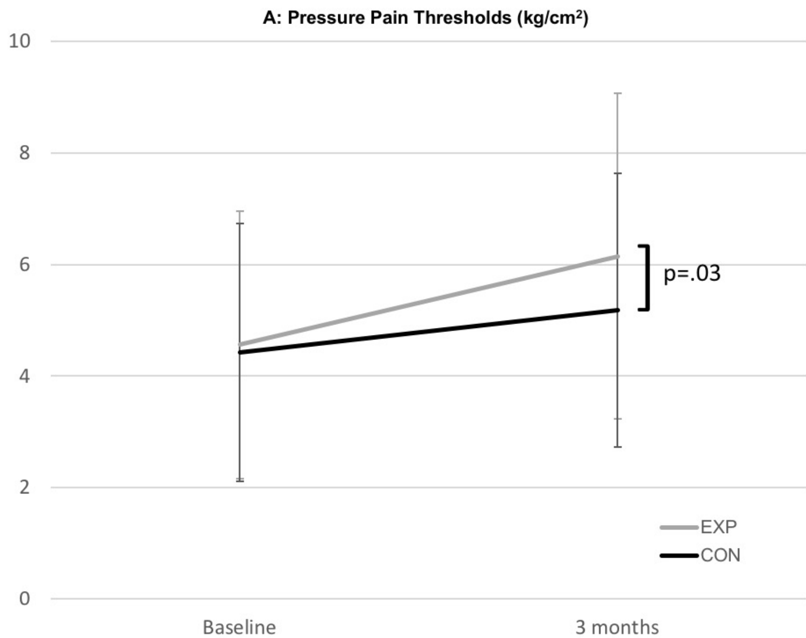
						[-.028,.056]					
Right hemisphere cortical thickness (mm)											
Caudal middle frontal	Base	2.555±.016	-	2.540±.016	-	.015 [-.029,.059]					
	3mo	2.559±.016	+.15%	2.525±.016	-.59%	.034 [-.010,.078]	F=2.502 p=.09	F=1.071 p=.35			
	12mo	2.545±.016	-.55%	2.522±.016	-.12%	.022 [-.022,.066]					
Inferior parietal	Base	2.563±.017	-	2.541±.017	-	.022 [-.024,.069]					
	3mo	2.557±.018	-.23%	2.527±.018	-.55%	.029 [-.021,.080)	F=2.658 p=.08	F=.236 p=.79			
	12mo	2.554±.016	-.12%	2.528±.016	+.04%	.026 [-.020,.072]					
Inferior temporal	Base	2.817±.017	-	2.805±.017	-	.012 [-.036,.061]				Time	12mo<Base **p=.004**[b]
	3mo	2.817±.018	-	2.794±.018	-.39%	.023 [-.026,.072]	F=6.097 **p=.003**	F=1.094 p=.34			
	12mo	2.805±.018	-.43%	2.776±.018	-.64%	.029 [-.021,.079]					
Medial orbito-frontal	Base	2.323±.023	-	2.309±.023	-	.014 [-.050,.078]					
	3mo	2.332±.027	+.39%	2.290±.027	-.82%	.042 [-.033,.118]	F=1.078 p=.35	F=1.425 p=.25			
	12mo	2.333±.027	+.04%	2.321±.027	+1.35%	.012 [-.063,.086]					
Parahippo-campal	Base	2.824±.032	-	2.811±.032	-	.013 [-.076,.102]					
	3mo	2.820±.034	-.14%	2.788±.034	-.82%	.031 [-.065,.128]	F=1.897 p=.16	F=1.174 p=.31			
	12mo	2.830±.033	+.35%	2.801±.033	+.47%	.029 [-.064,.122]					
Postcentral	Base	2.183±.015	-	2.173±.015	-	.010 [-.053,.032]	F=5.988 p=.004	F=1.829 p=.17		Time	12mo<Base **p=.006**[b]
	3mo	2.191±.017	+.37%	2.162±.017	-.51%	.029 [-.019,.078]					

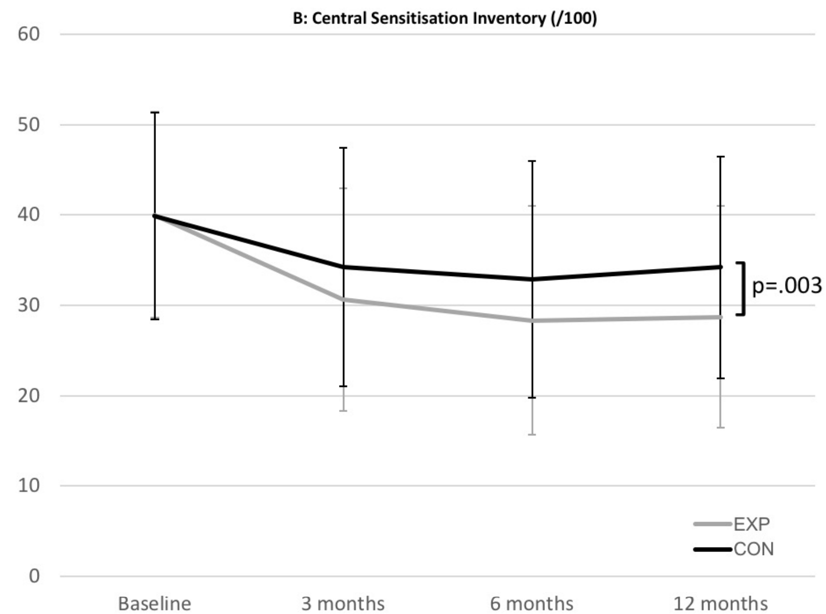
	12mo	2.177±.016	-.64%	2.152±.016	-.46%	.025 [-.020,.070]					
Precentral	Base	2.625±.017	-	2.571±.017	-	.054 [-.102,-.005]				Group	Base: **p=.03** 3mo: **p=.03** 12mo: **p=.01**
	3mo	2.624±.019	-.04%	2.564±.019	-.27%	.060 [.007,.112]	F=4.479 **p=.01**	F=.333 p=.72			
	12mo	2.614±.018	-.38%	2.552±.018	-.47%	.062 [.013,.111]				Time	12mo<Base **p=.05**[b]
Rostral middle frontal	Base	2.270±.015	-	2.266±.015	-	.004 039,.047]					
	3mo	2.285±.017	+.66%	2.257±.017	-.40%	.028 [-.019,.074]	F=.209 p=.81	F=1.961 p=.15			
	12mo	2.271±.017	-.61%	2.263±.017	+.27%	.008 [-.039,.054]					
Superior parietal	Base	2.273±.014	-	2.260±.014	-	.013 [-.026,.051]					
	3mo	2.269±.016	-.18%	2.244±.016	-.71%	.026 [-.018,.069]	F=2.416 p=.10	F=.796 p=.46			
	12mo	2.264±.014	-.22%	2.247±.014	+.13%	.017 [-.023,.057]					
Supra-marginal	Base	2.654±.015	-	2.629±.015	-	.025 [-.067,.017]				Group	Base: p=.239 3mo: **p=.05** 12mo: **p=.03**
	3mo	2.660±.016	+.23%	2.614±.016	-.57%	.046 [.000,.093]	F=7.873 **p=.001**	F=3.341 **p=.04**			
	12mo	2.646±.015	-.53%	2.598±.016	-.61%	.049 [.005,.092]				Time	12mo<Base **p<.001** [b]
Left hemisphere subcortical volumes (mm^3)											
Amygdala	Base	1628.972± 27.464	-	1615.457± 27.245	-	13.516 [-63.117,90.148]					
	3mo	1627.242± 29.188	-.10%	1613.691± 29.130	-.11%	13.551 [-68.125,95.227]	F=.033 p=.97	F=.056 p=.95			
	12mo	1625.975± 27.896	-.08%	1615.926± 27.802	+.14%	9.869 [-69.139,87.877]					
Caudate	Base	3771.990± 61.461	-	3856.723± 60.942	-	-84.733 [-256.180,86.711]	F=19.205 **p<.001**	F=1.403 p=.25		Time	12mo<Base **p=.003**[a] Base>3mo,Base
	3mo	3762.799±	-.24%	3831.726±	-.65%	-68.927					

		61.317		60.840		[-240.020,102.168]					**p=.010, p<.001**[b]
	12mo	3744.945± 60.344	-.47%	3814.055± 59.888	-.46%	-69.110 [-237.510,99.287]					
Hippocampus	Base	4259.190± 50.740	-	4239.139± 50.320	-	20.051 [-121.500,161.601]	F=.073 p=.93	F=.310 p=.74			
	3mo	4257.386± 54.058	-.04%	4236.183± 53.706	-.07%	21.203 [-129,740,172.144]					
	12mo	4262.506± 52.900	+.12%	4229.784± 52.602	-.15%	32.722 [-115.050,180.493]					
Putamen	Base	5837.205± 88.902	-	5736.388± 88.165	-	100.818 [-147.200,348.833]	F=3.258 **p=.043**	F=.846 p=.43		Time	12mo<Base **p=.03**[a]
	3mo	5816.908± 89.305	-.35%	5719.808± 88.691	-.29%	97.099 [-152.210,346.409]					
	12mo	5785.682± 86.948	-.54%	5716.809± 86.434	-.05%	68.872 [-173.990,311.735]					
Thalamus*	Base	8185.162± 126.307	-	8348.874± 126.307	-	-163.712 [-517.566,190.142]	F=.001 p=.99	F=.043 p=.96			
	3mo	8217.104± 132.604	+.39%	8303.986± 137.152	-.54%	-86.882 [-466.064,292.300]					
	12mo	8202.495± 138.960	-.18%	8202.495± 138.960	-.02%	-125.279 [-526.266,275.708]					
Right hemisphere subcortical volumes (mm^3)											
Amygdala	Base	1578.702± 25.125	-	1578.801± 24.932	-	-.099 [-70.212,70.014]	F=.156 p=.87	F=1.430 p=.25			
	3mo	1591.495± 25.994	+.81%	1571.365± 25.920	-.47%	-20.130 [-52.577,92.836]					
	12mo	1578.295± 26.531	-.83%	1576.724± 26.633	+.34%	1.571 [-72.889,76.031]					
Caudate	Base	3843.967± 66.509	-	3925.785± 66.950	-	-82.089 [-267.62,103.441]	F=7.659 **p=.001**	F=.808 p=.45		Time	12mo<Base **p=.002**[a]
	3mo	3822.221± 66.811	-.57%	3909.923± 66.300	-.40%	-87.702 [-274.140,98.740]					
	12mo	3805.259± 64.998	-.44%	3907.186± 65.544	-.07%	-101.930 [-283.370,79.513]					
Hippocamp	Base	4347.690± 54.489	-	4288.487± 54.035	-	59.203 [-92.802,211.207]	F=3.420 **p=.04**	F=.550 p=.58		Time	NS

us	3mo	4342.358± 54.642	-.12%	4267.886± 54.260	-.48%	74.473 [-78.058,227.004]					
	12mo	4330.651± 54.494	-.27%	4265.546± 54.151	-.05%	65.105 [-87.066,217.276]					
Putamen	Base	5485.871± 81.086	-	5374.525± 80.411	-	111.346 [-114.860,337.550]				Time	12mo<Base **p=.03**[a] 3mo<Base **p=.04**[b]
	3mo	5459.931± 80.223	-.47%	5335.155± 79.657	-.74%	124.776 [-99.168,348.719]	F=5.921 **p=.004**	F=1.245 p=29			
	12mo	5438.656± 82.317	-.39%	5356.033± 81.840	+.39%	82.623 [-147.320,312.568]					
Thalamus	Base	7431.581± 101.900	-	7312.849± 101.050	-	118.732 [-165.530,402.995]				Time	12mo<base **p=.05**[a]
	3mo	7411.898± 100.740	-.26%	7311.644± 100.006	-.02%	100.254 [-180.920,381.426]	F=5.712 **p=.005**	F=.316 p=.73			
	12mo	7377.088± 104.319	-.47%	7264.063± 103.692	-.65%	113.025 [-178.320,404.369]					

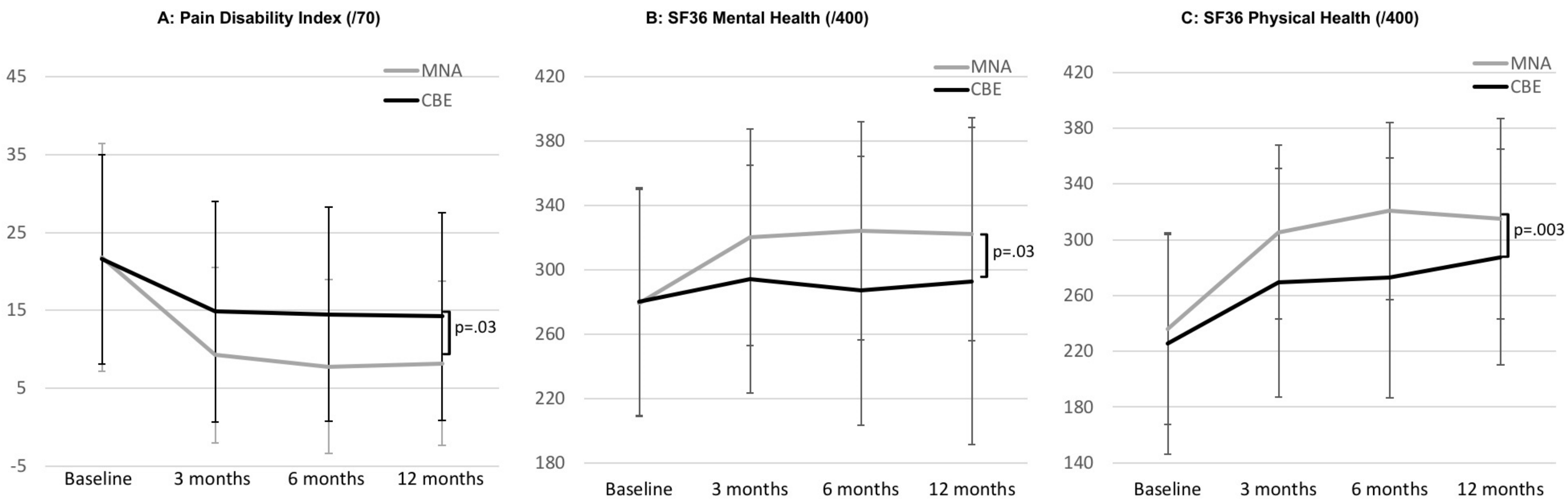
All analyses were performed using Linear Mixed Models. When a variable was assessed for more than two times 'repeated covariance type' was set at 'unstructured'. In regions with (*), convergence could not be achieved and 'repeated covariance type' was set at 'diagonal'.
Experimental treatment = pain neuroscience education combined with cognition-targeted motor control training; control treatment = current best evidence physiotherapy
Significant p-values, clinical significant improvements and large to very large effect sizes were printed in **bold**.
[a]=Results of Bonferroni Post-Hoc tests in the Modern Neuroscience Group; [b]=Results of Bonferroni Post-Hoc tests in the current best evidence physiotherapy group
Abbreviations: SD= Standard Deviation; Base= Baseline measurement; 3mo= Measurement at 3 months follow-up; 12mo= Measurement at 12 months follow-up





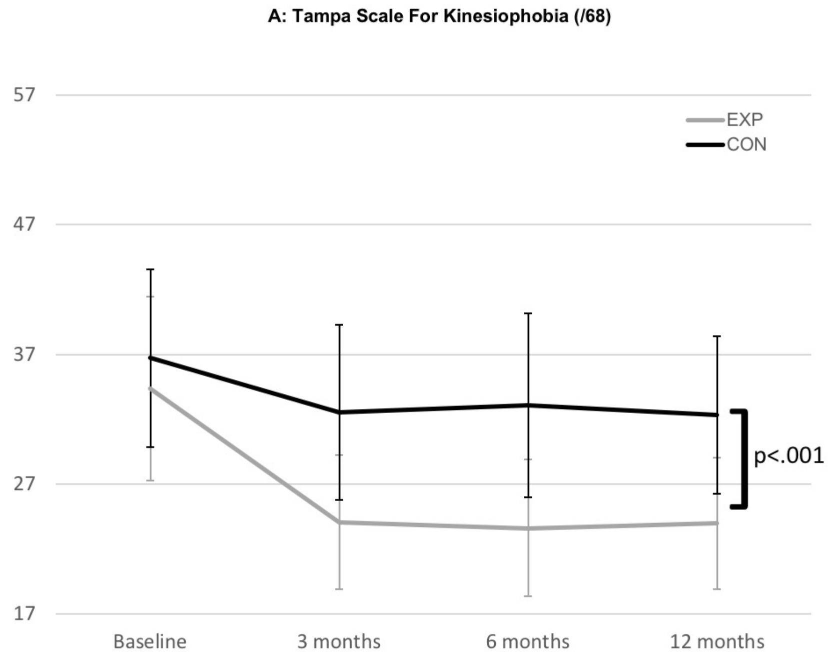
eFigure 1: Pain neuroscience education combined with cognition-targeted motor control training (EXP) is effective for increasing pain pressure thresholds (A) and for reducing self-reported symptoms of hypersensitivity for non-musculoskeletal stimuli (B; central sensitization inventory), compared to current best evidence physiotherapy (CON) in patients with chronic spinal pain (n=120).

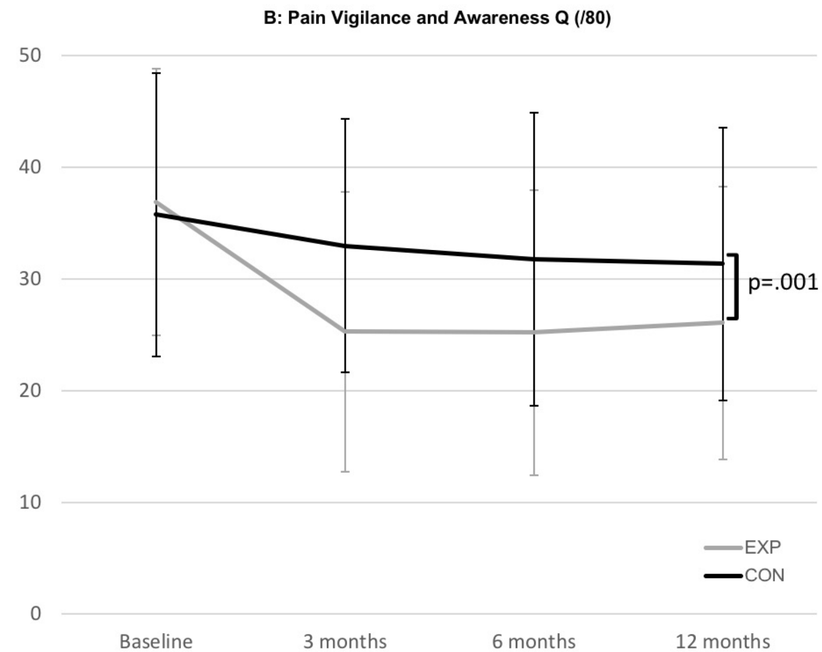
P-values at the right side of the graph represent significant interaction effects. For detailed results: see table 2. A: Significant increase in the modern neuroscience approach group ($p<.001$) and current best evidence physiotherapy group ($p=.009$). B: Significant higher CSI levels at baseline when compared to 3 months, 6 months and 12 months follow-up in the modern neuroscience approach group ($p<.001$) and the current best evidence physiotherapy group ($p<.003$). Additionally, at 6 months ($p=.02$) and 12 months ($p=.01$) significant lower CSI-levels in the modern neuroscience group compared to the current best evidence physiotherapy group.



eFigure 2: Pain neuroscience education combined with cognition-targeted motor control training (EXP) is effective for reducing disability (A), for increasing perceived mental health (B) and for increasing perceived physical health (C), compared to current best evidence physiotherapy (CON) in patients with chronic spinal pain (n=120).

P-values at the right side of the graph represent significant interaction effects. For detailed results: see table 2. A: Significant lower disability levels at baseline when compared to 3 months, 6 months and 12 months follow-up in the modern neuroscience group (p<.001) and the current best evidence physiotherapy group (p<.001). Additionally, at 3 months (p=.04), 6 months (p=.01) and 12 months (p=.01) significant lower levels in the modern neuroscience group compared to the current best evidence physiotherapy group. B: Significant higher mental health levels at baseline when compared to 3 months, 6 months and 12 months follow-up in the modern neuroscience group (p<.001) and the current best evidence physiotherapy group (p<.001). Additionally, at 6 months (p=.01) significant higher levels in the modern neuroscience group compared to the current best evidence physiotherapy group. C: Significant higher physical health levels at baseline when compared to 3 months, 6 months and 12 months follow-up in the modern neuroscience group (p<.001) and the current best evidence physiotherapy group (p<.001). Additionally, at 3 months (p=.009) 6 months (p<.001) and at 12 months (p=.03) significant higher levels in the modern neuroscience group compared to the current best evidence physiotherapy group.





eFigure 3: Pain neuroscience education combined with cognition-targeted motor control training (EXP) is effective for reducing fear of movement pain pressure thresholds (A) and for reducing pain vigilance and awareness (B), compared to current best evidence physiotherapy (CON) in patients with chronic spinal pain (n=120).

P-values at the right side of the graph represent significant interaction effects. For detailed results: see table 2. A: Significant lower levels of fear of movement at baseline when compared to 3 months, 6 months and 12 months follow-up in the modern neuroscience group ($p<.001$) and the current best evidence physiotherapy group($p<.007$). Additionally, at 3 months ($p<.001$), 6 months ($p<.001$) and 12 months ($p<.001$) significant lower levels in the modern neuroscience group compared to the current best evidence physiotherapy group. B: Significant lower pain vigilance and awareness levels at baseline when compared to 3 months, 6 months and 12 months follow-up in the modern neuroscience group ($p<.001$) and the current best evidence physiotherapy group ($p<.001$). Additionally, at 3 months ($p=.001$), 6 months ($p=.005$) and 12 months ($p=.01$) significant lower levels in the modern neuroscience group compared to the current best evidence physiotherapy group.