Supplementary Information

Corticostriatal functional connectivity predicts transition to chronic back pain

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Supplementary information contains:

1. Supplementary text

2. Supplementary Figs 1–9

3. Supplementary Tables 1–4

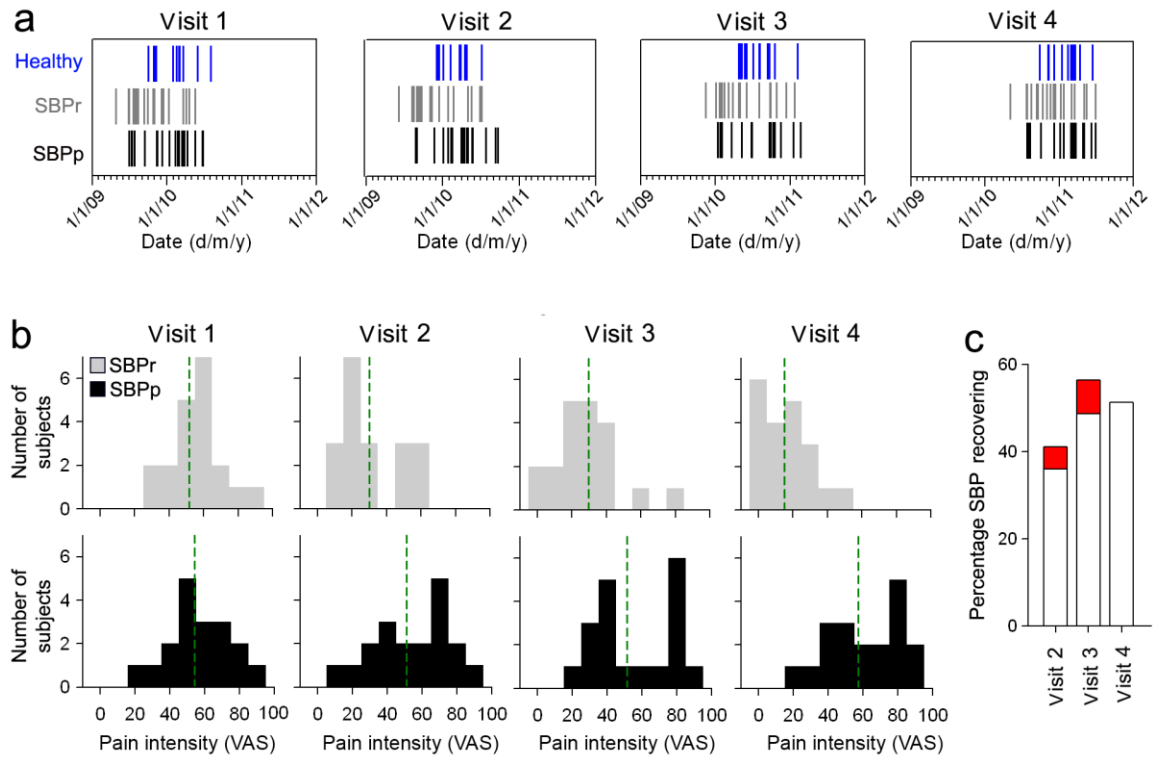
Supplementary text

Supplementary Figure 1 and Supplementary Tables 1 and 2A expand the results shown in **Fig. 1a**, presenting the changes in back pain and related questionnaire–based characteristics of SBPp and SBPr patients in time. **Supplementary Figure 2** expands upon the results shown in **Fig. 1b** and show the relationship between gray matter volume and age and gender, as well as detailed statistical comparisons for differences in mean gray matter volume between groups and visits and their relationship to age and gender using repeated measure ANCOVA, with gender and age treated as confounds. **Supplementary Figure 3** shows the detailed maps for the whole–brain voxelwise repeated measures ANOVA for gray matter density changes longitudinally across visits, for the SBPr, SBPp and healthy controls, complementing **Fig. 1c.** Peak coordinates for the ANOVA–s are shown in **Supplementary Table 3**.

Supplementary Figure 4 shows time–courses of gray matter density changes for all regions identified to undergo longitudinal changes in **Supplementary Figure 3**. Results for right NAc and right insula are the same as shown in **Fig. 1d**. Note that right MTG is the region commonly decreasing across all three groups, and this change is attributed to aging. Comparisons of regional gray matter density between groups and visits were also calculated using repeated measure analysis of covariance (ANCOVA). Functional connectivity maps for the NAc, insula and S1/M1 regions of interest are shown in **Supplementary Figures 5–7 respectively.** In each case, contribution of age and gender are also shown. **Supplementary Figure 8** shows group–averaged head motion for functional scans collected at visit 1 and visit 4. In general head movement for all groups was small (~ 1 mm) and there were no significant differences between groups.

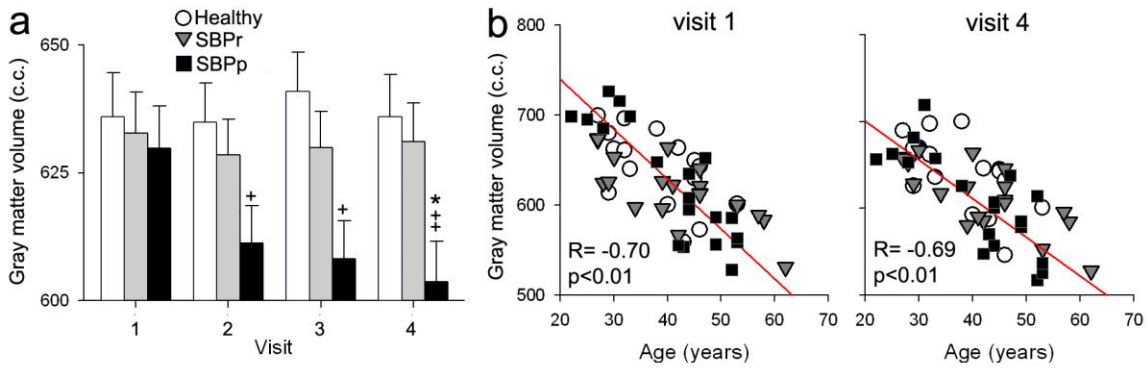
In addition to head motion parameters, signal to noise ratios (SNR) of T1–anatomical images are shown. SNR was neither different in time nor across groups. Moreover, relationship between head movement and functional connectivities are listed, showing no significant relationship. **Supplementary Figure 9** shows detailed information on drug usage. There were no differences in drug usage in time or across groups. In addition, drug usage did not correlate with any functional or anatomical measurements for any group or visit.

Supplementary Table 1 shows that age, gender and education levels were equivalent between healthy controls, SBP, and the validation SBP. **Supplementary Table 2B** shows pain related characteristics for the cohort of SBP used for validation. In this group, similar to the original SBP group, SBPp and SBPr had similar pain properties at visit 1 but diverged at visit 4. **Supplementary Table 4A** shows odds ratios for mPFC–NAc functional connectivity, for nine pain and mood questionnaires, and for early drug use outcomes, when each of these parameters at visit 1 was used to predict SBPp and SBPr at visit 4. The best predictor was mPFC–NAc functional connectivity, followed by pain duration, while sensory pain and early drug use approached significance. These four parameters were used to build a hierarchical multiple regression logistic models, where pain duration was not significant any more and was removed. The final model is shown in **Supplementary Table 4B**. The model shows that the dominant predictor for transition to chronic pain is mPFC–NAc functional connectivity. Moreover, early drug use (i.e. SBP patients who were already using analgesics at entry into the study) was protective against transition to chronic pain.



Supplementary Figure 1. Changes in back pain characteristics over 1 year in SBP patients

(a) Plots depict the scanning calendar dates of healthy, SBPr and SBPp subjects for all visits, expanded from **Fig. 1a**. Vertical marks represent individual subjects, color–coded by group. Groups were scanned within the same time window (X–axis major ticks are years; minor ticks are months). The distribution of times at all four visits are random across groups, eliminating the potential bias of scan order. **(b)** Pain intensity histogroms for SBPr and SBPp at all visits. SBPr and SBPp exhibit similar and overlapping pain distributions at visit 1, which diverge in subsequent visits. Dotted green line represents the mean. **(c)** Percentage of SBP patients recovering since visit 1. Red bars are percentage of patients that exhibited reversal from recovery and were classified as persisting SBP at visit 4. Only 4–5% of the subjects switch categories in the intermediate visits.



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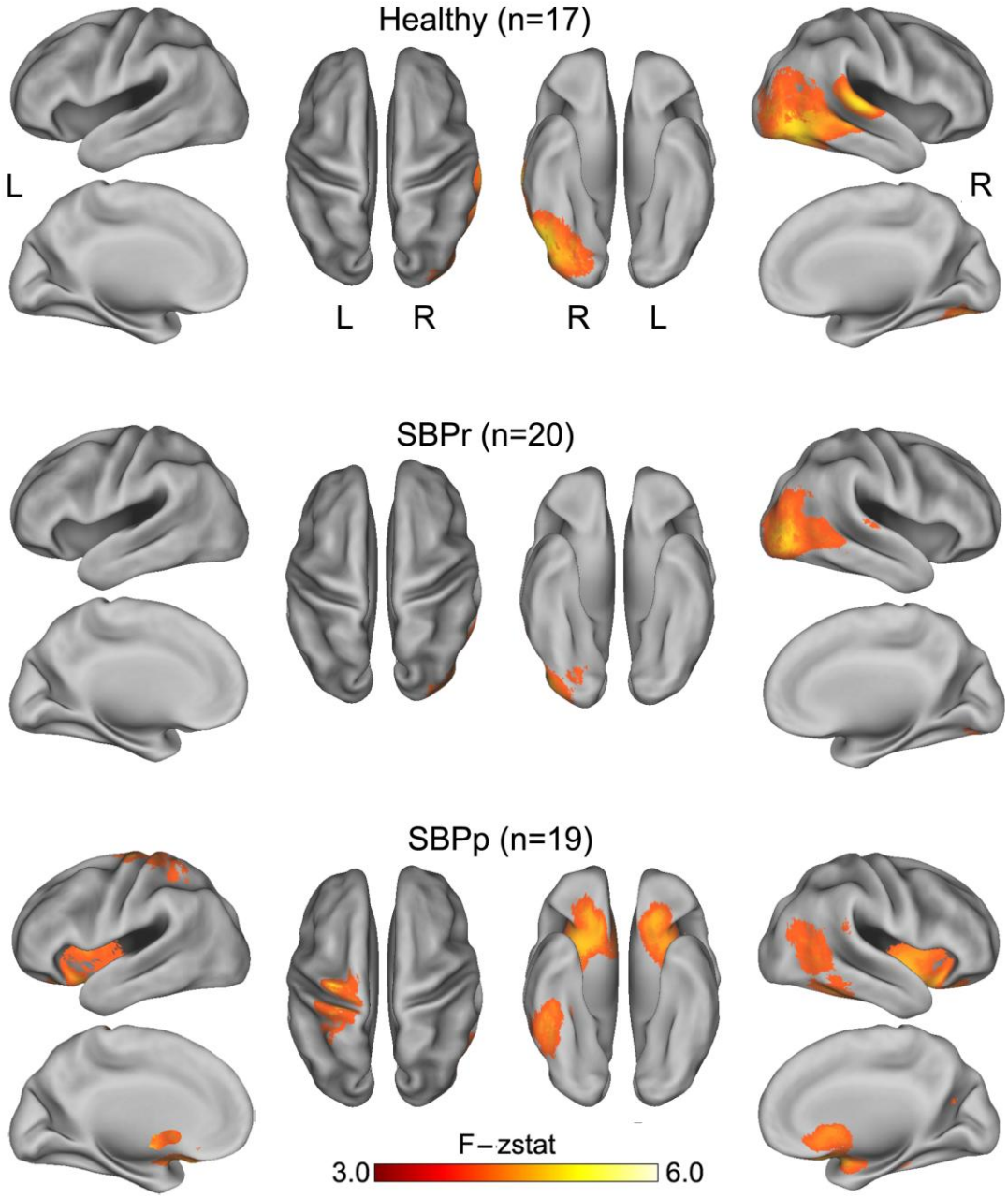
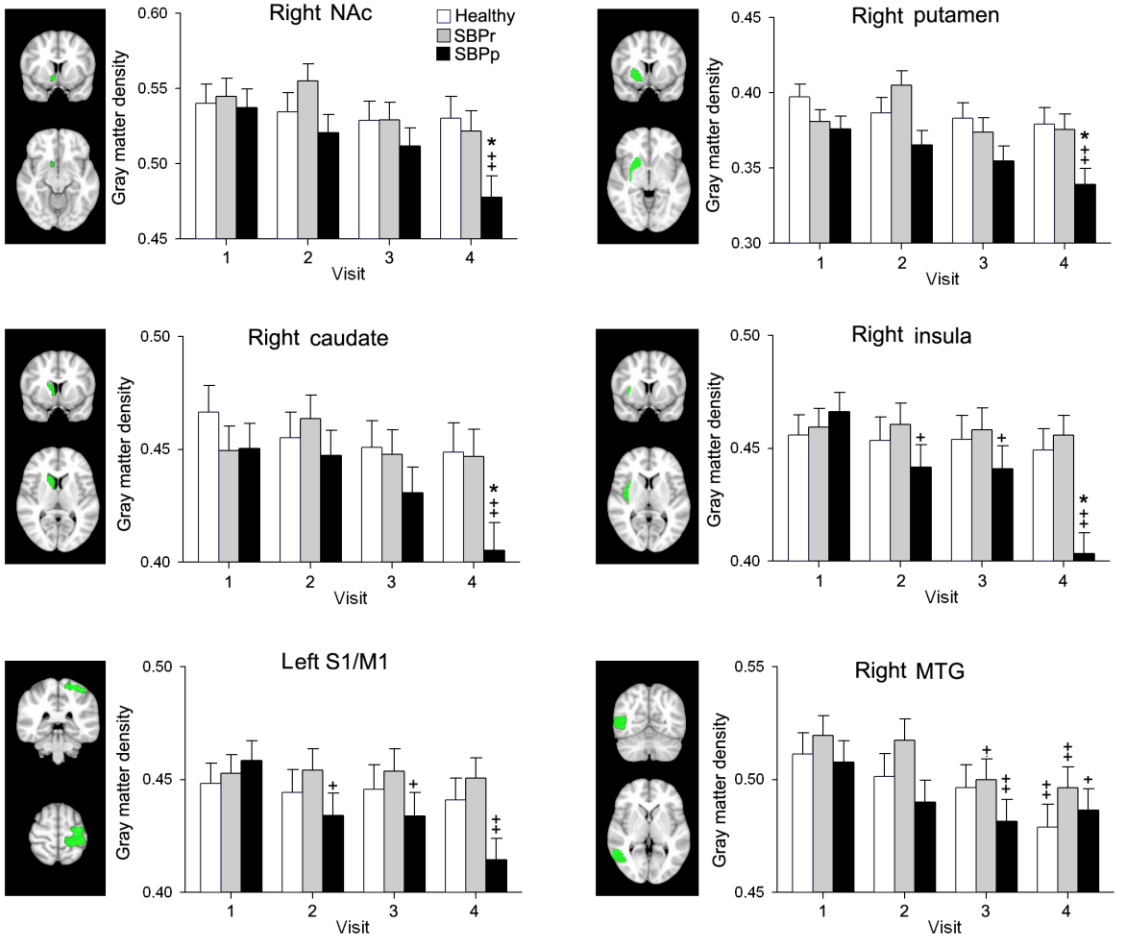
	All Subjects R (p-value)	Healthy R (p-value)	SBPr R (p-value)	SBPp R (p-value)
Visit 1	-0.70 (<0.01)	-0.59 (<0.01)	-0.63 (<0.01)	-0.86 (<0.01)
Visit 2	-0.67 (<0.01)	-0.58 (<0.01)	-0.75 (<0.01)	-0.66 (<0.01)
Visit 3	-0.67 (<0.01)	-0.55 (<0.05)	-0.80 (<0.01)	-0.66 (<0.01)
Visit 4	-0.69 (<0.01)	-0.62 (0.01)	-0.61 (<0.01)	-0.83 (<0.01)

Supplementary Figure 2. Global neocortical gray volume changes over 1 year in SBP patients and healthy controls.

(a) Bar graphs depict the mean±SEM neocortical gray matter volume across groups and visits. Defferences in gray matter volumes between group and visits were computed using a repeated measure ANCOVA, with gender and age as confounds (from **Fig. 1b**). changes in gray matter volume showed a significant effect for interaction for group and visit (Group $F_{(2,49)}$=2.95, p=0.06; Visit $F_{(3,147)}$=2.27, p=0.08; Group*Visit $F_{(6,147)}$=3.23, p<0.01). In addition gray matter volume showed high dependence with age ($F_{(3,147)}$=53.38, p<0.01) and gender ($F_{(3,147)}$=4.43, p<0.05). Error bars are S.E.M. **(b)** Scatter plot presents neocortical gray matter volume in relation to age for each subject, color–coded by group for visit 1 and visit 4. **(c)** Relationship between neocortical gray matter volume and age across all visits. Correlations were computed for all subjects and each group separately. All groups showed a significant negative correlation between neocortical gray matter volume and age.



Supplementary Figure 3. Changes in regional gray matter density over 1 year in SBP patients and healthy controls.
Detailed maps for whole–brain voxelwise repeated measures ANOVA for gray matter density changes across visits for the SBPr, SBPp and healthy controls expanding results shown in **Fig. 1c**. Regions shown in red–yellow represent voxels that showed significant change in gray matter density between visits (random–effects model, F–zstat > 3.0, cluster $p < 0.01$, corrected for multiple comparisons). Healthy subjects and SBPr showed minimal changes in gray matter density localized to right temporal cortex. SBPp showed extensive changes within multiple regions including: bilateral NAc, caudate, putamen and insula in addition to left S1/M1 area and right temporal cortex. List of regions and their respective coordinates are presented in **Supplementary Table 3**.

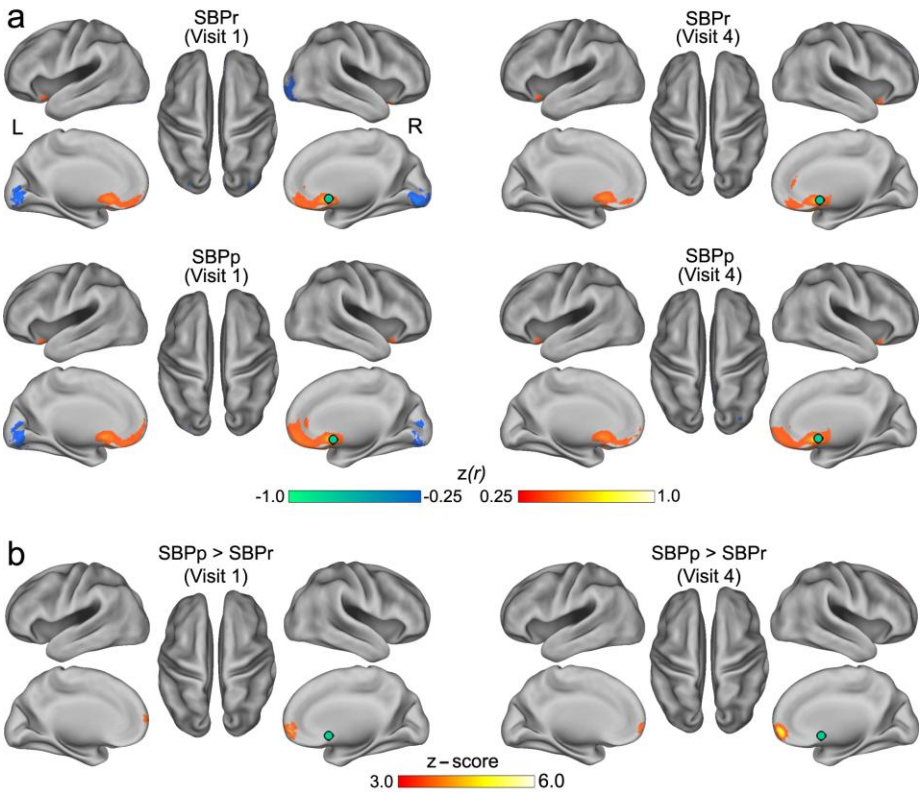


	NAc F (p-value)	Putamen F (p-value)	Caudate F (p-value)	Insula F (p-value)	S1/M1 F (p-value)	MTG F (p-value)
Group	1.65 (0.20)	3.32 (<0.05)	1.26 (0.29)	1.68 (0.20)	1.09 (0.34)	1.01 (0.37)
Visit	4.70 (<0.01)	3.82 (<0.05)	2.28 (0.08)	0.62 (0.61)	0.29 (0.83)	3.37 (<0.05)
Group*Visit	3.57 (<0.01)	2.97 (<0.01)	3.63 (<0.01)	6.88 (<0.01)	3.72 (<0.01)	1.64 (0.14)
Age	14.52 (<0.01)	10.47 (<0.01)	10.41 (<0.01)	11.68 (<0.01)	10.98 (0.72)	5.91 (<0.01)
Gender	0.40 (0.75)	0.25 (0.62)	0.08 (0.78)	1.98 (0.15)	2.42 (0.10)	3.37(<0.05)

aROI	Center of gravity x (mm)	y(mm)	z(mm)	Size (voxels)
NAc	9.86	12.07	-7.62	86
putamen	24.41	7.58	-4.01	444
caudate	12.76	14.25	5.65	323
Insula	38.67	-2.85	1.89	597
S1/M1	-27.08	-26.63	67.96	401
MTG	51.63	-60.14	3.85	687

Supplementary Figure 4. Regional gray matter density changes over 1 year in SBP patients and healthy controls.

Region of interest (ROI) analysis for brain areas that showed significant changes in time in relation to visit 1 **(Fig. 1d, Supplementary Figure 3).** Defferences in changes between group and visits were computed using a repeated measure ANCOVA, with gender and age as confounds. Brain images depict the corresponding anatomical ROI (aROI), which is shown in green. Bar graphs show the mean±S.E.M. gray matter density for all groups and visits. Left table shows the effects for group, visits (time), and their interaction. All regions showed a signifecent group*visit effect except fot middle temporal gyrus (MTG) which showed similar decreases across all groups. In addition age showed signifecent effects for all ROIs examined, while gender showed a signifenct effect only for MTG. Right table displays the coordinates of the center of gravity for each aROI and its respective size. [+p<0.05, ++p<0.01, within group comparison to visit 1; *p<0.05, **p<0.01 comparison to Healthy at corresponding time]. Error bars are S.E.M.



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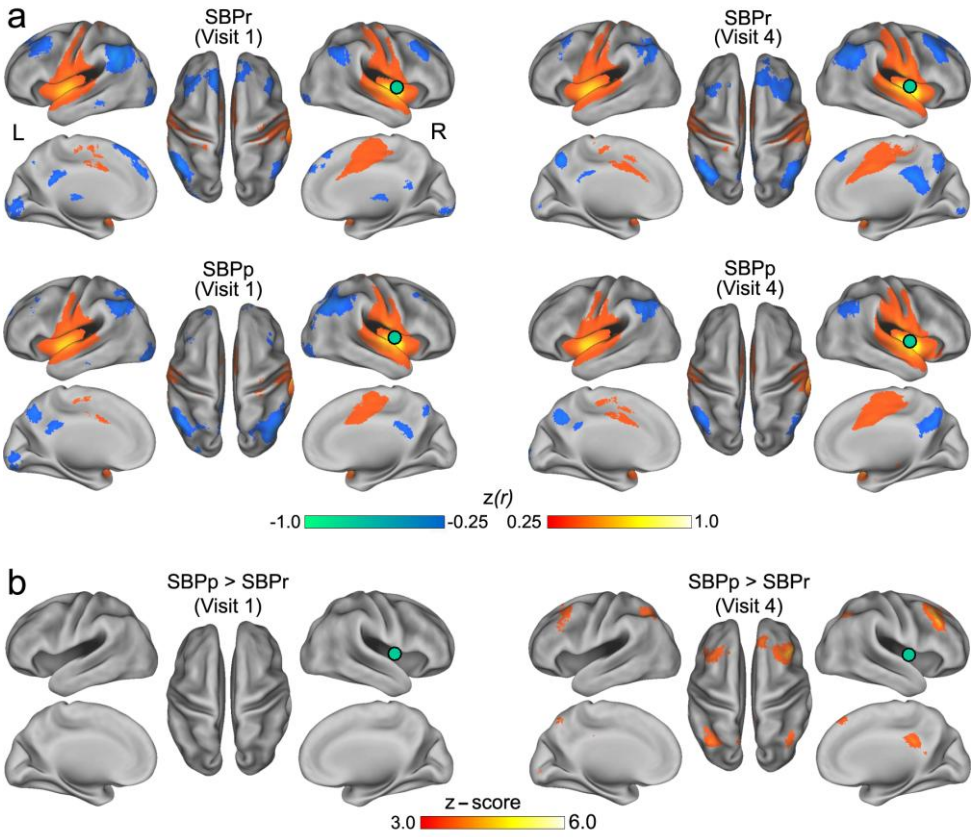
	Visit 1		Visit 4	
	Gender R (p-value)	Age R (p-value)	Gender R (p-value)	Age R (p-value)
SBPr positive links	-0.03 (0.91)	-0.17 (0.46)	-0.39 (0.09)	0.24 (0.31)
SBPr negative links	-0.23 (0.31)	-0.09 (0.69)	-0.43 (0.06)	-0.16 (0.49)
SBPp positive links	-0.30 (0.29)	0.28 (0.24)	-0.10 (0.67)	0.13 (0.61)
SBPp negative links	-0.26 (0.28)	0.18 (0.46)	1.92 (0.72)	0.60 (<0.01)

Supplementary Figure 5. Group differences in NAc functional connectivity between SBPr and SBPp

(a) Group average functional connectivity maps for the right NAc region of interest (green circle) during a self–report pain–rating task are shown for SBPr and SBPp at visit 1 and visit 4,. Regions with positive correlations (red–yellow) have z scores > 2.3 ($p < 0.01$), and those with negative correlations (blue–green) have z scores < −2.3 ($p < 0.01$). In general the NAc showed postive correlation to areas within the straitum, the most anterior parts of the cingulate cortex and the medial prefrontal cortex (mPFC). **(b)** Detailed maps for the whole–brain voxelwise contrast of NAc functional connectivity between SBPp and SBPr **(Fig. 2a)**. Brain regions in red–yellow depict statistically significant differences (random–effects model, z–score > 3.0, cluster $p < 0.01$, corrected for multiple comparisons). SBPp showed significantly higher positive correlation between NAc and mPFC at visit 1 and visit 4. **(c)** Table shows the relationship between postive and negative functional connections **(Fig. 2b)** with age and gender at both visits. Functional coonectivity did not exhibit any signifecant dependence on gender, while only the negative links in SBPp showed a relationship with age at visit 4 (p–values uncorrected).



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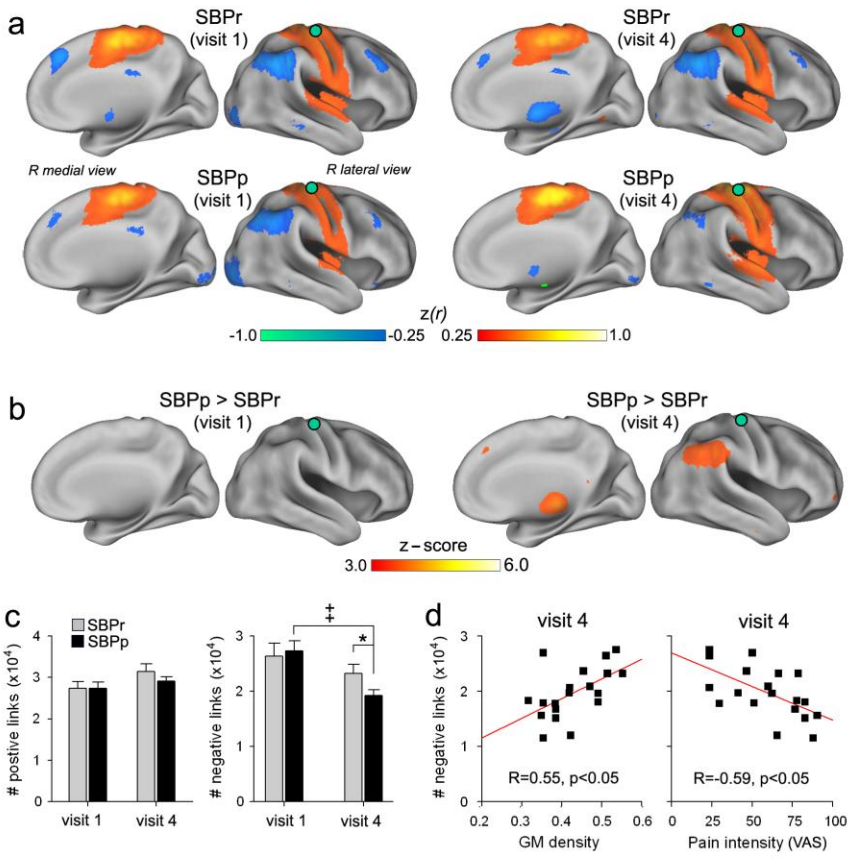
	Visit 1		Visit 4	
	Gender R (p-value)	Age R (p-value)	Gender R (p-value)	Age R (p-value)
SBPr positive links	-0.32 (0.16)	-0.17 (0.46)	0.02 (0.92)	0.10 (0.69)
SBPr negative links	0.26 (0.26)	-0.18 (0.43)	-0.12 (0.67)	0.33 (0.15)
SBPp positive links	0.36 (0.13)	0.37 (0.12)	-0.11 (0.68)	-0.06 (0.82)
SBPp negative links	-0.48 (<0.05)	0.13 (0.60)	-0.08 (0.74)	-0.17 (0.49)

Supplementary Figure 6. Group differences in insula functional connectivity between SBPr and SBPp

(a) Group average functional connectivity maps for the right insula region of interest (green circle) during a self–report pain–rating task are shown for SBPr and SBPp at visit 1 and visit 4. Regions with positive correlations (red–yellow) have z–scores >2.3 ($p < 0.01$), and those with negative correlations (blue–green) have z–scores < −2.3 ($p < 0.01$). In general the insula showed postive correlation with sensory regions and negative correlation with multiple frontal and posterior parietal regions in addition to the poster cingulate cortex. **(b)** Detailed maps for the whole–brain voxelwise contrast of insula functional connectivity between SBPp and SBPr **(Fig. 2d)**. Brain regions in red–yellow depict statistically significant changes (random–effects model, z–score > 3.0, cluster $p < 0.01$, corrected for multiple comparisons). SBPp showed decreased negative correlations of insula with dorsolateral prefrontal cortex and posterior cingulate cortex at visit 4. **(c)** Table shows the relationship between postive and negative functional connections **(Fig. 2e)** with age and gender at both visits. Functional coonectivity did not exhibit any signifecant dependence on age, while only the negative links in SBPp showed a relationship with gender at visit 1 (p–values uncorrected).

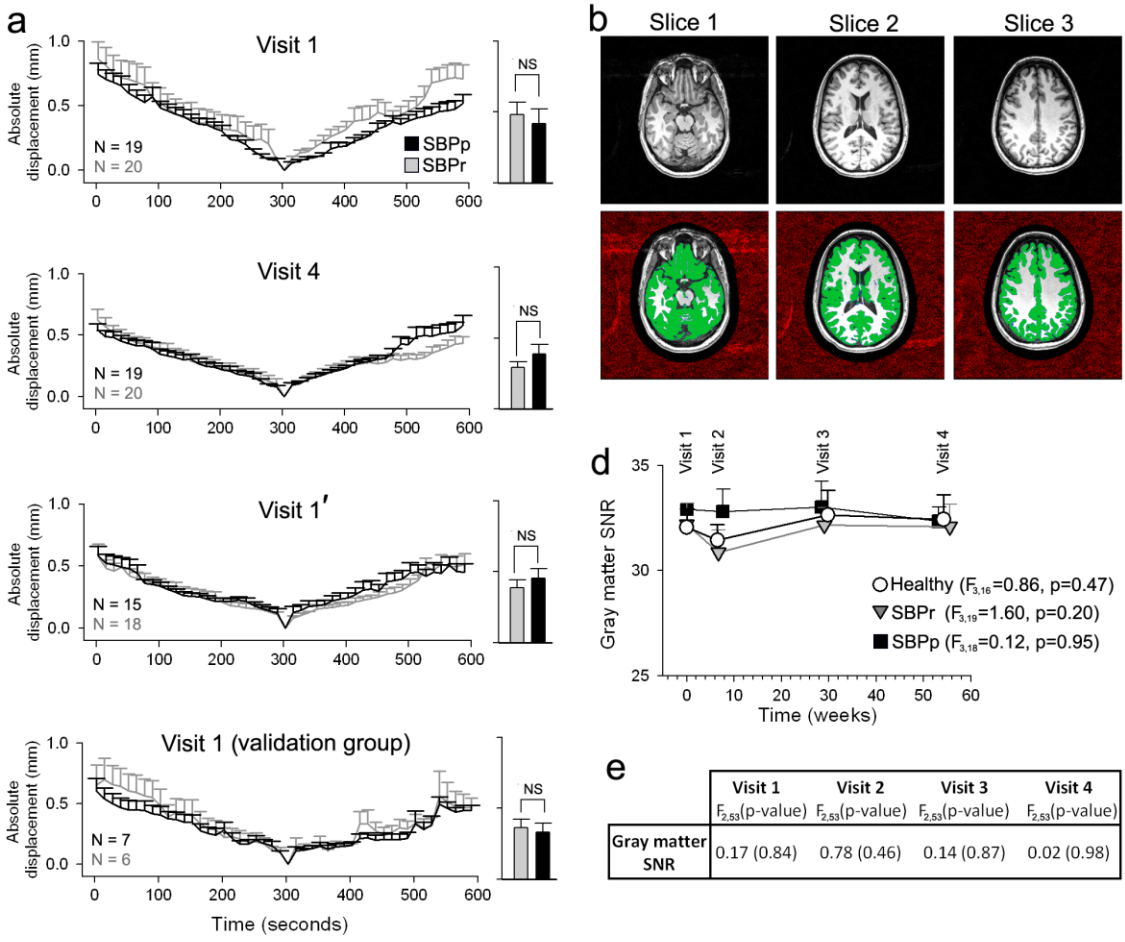


e

	Visit 1		Visit 4	
	Gender R (p-value)	Age R (p-value)	Gender R (p-value)	Age R (p-value)
SBPr positive links	-0.14 (0.57)	-0.07 (0.78)	-0.02 (0.91)	0.29 (0.21)
SBPr negative links	0.09 (0.71)	-0.05 (0.83)	-0.09 (0.71)	0.39 (0.09)
SBPp positive links	0.22 (0.37)	0.06 (0.80)	-0. 01 (0.98)	-0.43 (0.06)
SBPp negative links	0.06 (0.82)	0.21 (0.39)	-0.35 (0.15)	-0.15 (0.55)

Supplementary Figure 7. S1/M1 exhibits late functional reorganization similar to that seen in insula

(a) Group average functional connectivity maps for the right S1/M1 region of interest (green circle) during a self–report pain–rating task are shown for SBPr and SBPp at visit 1 and visit 4. Regions with positive correlations (red–yellow) have z–scores >2.3 ($p < 0.01$), and those with negative correlations (blue–green) have z–scores < −2.3 ($p < 0.01$). **(b)** Whole–brain voxelwise contrast of S1/M1 connectivity between SBPp and SBPr. Brain regions in red–yellow depict statistically significant changes (unpaired t test, random–effects model, z–score > 3.0, cluster $p < 0.01$, corrected for multiple comparisons). SBPp showed decreased negative correlations of S1/M1 with bilateral thalamus and posterior parietal regions at visit 4. **(c)** Average number of voxels in SBPp and SBPr subjects exhibiting positive (*z(r)* >0.25) and negative (*z(r)* < –0.25) correlations at visits 1 and 4. SBPp showed decreased negative correlations at visit 4 with respect to both their own visit 1 and visit 4 SBPr. **(d)** Left scatter plot shows the relationship at visit 4 between the number of negative connections and gray matter density of the S1/M1. Decreased gray matter density in the S1/M1 showed a significant relationship to decreased number of negative links. Right scatter plots show the relationship between number of negative connections and pain intensity. **(e)** Table shows the relationship between postive and negative functional connections with age and gender at both visits. Functional connectivity did not exhibit any significant dependence with either parameter. [*p<0.05 in comparison to SBPr], [++p<0.01 in comparison to visit 1]. Error bars are S.E.M.



e

	Visit 1 $F_{2,53}$(p-value)	Visit 2 $F_{2,53}$(p-value)	Visit 3 $F_{2,53}$(p-value)	Visit 4 $F_{2,53}$(p-value)
Gray matter SNR	0.17 (0.84)	0.78 (0.46)	0.14 (0.87)	0.02 (0.98)

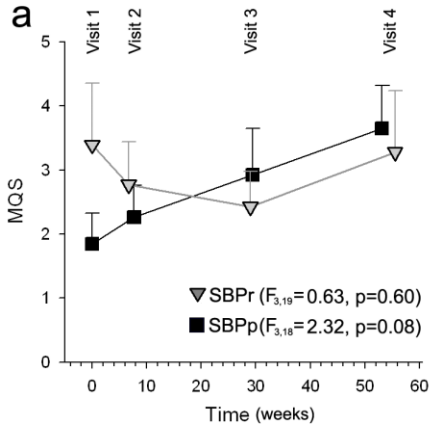
f

	Visit 1		Visit 4		Visit 1′		Visit 1 (validation)	
	SBPr R (p-value)	SBPp R (p-value)	SBPr R (p-value)	SBPr R (p-value)	SBPp R (p-value)	SBPp R (p-value)	SBPr R (p-value)	SBPp R (p-value)
NAc positive links	0.37(0.11)	-0.09 (0.71)	0.13 (0.58)	0.32 (0.18)				
NAc negative links	0.14(0.57)	0.34 (0.13)	0.23 (0.32)	0.46 (<0.05)				
insula positive links	-0.01(0.95)	0.33 (0.13)	0.12 (0.62)	0.20 (0.41)				
insula negative links	0.08(0.73)	-0.01 (0.95)	0.16 (0.51)	-0.14(0.56)				
S1/M1 positive links	0.01(0.96)	0.01 (0.96)	0.38 (0.10)	0.03 (0.89)				
S1/M1 negative links	-0.1 (0.68)	0.19 (0.40)	-0.21 (0.38)	-0.35 (0.14)				
NAc-mPFC *z(r)*	0.28(0.23)	0.14 (0.54)	-0.08 (0.73)	0.21 (0.38)	0.06(0.84)	-0.16(0.51)	0.09 (0.87)	-0.24(0.51)

Supplementary Figure 8. Motion artifacts and signal to noise ratio (SNR) comparisons.
(a) Time series plots depict absolute head displacement during functional scans which is estimated from the translational and rotational parameters obtained by rigid body correction of head motion. Head displacement relative to its position mid way through the scan (t = 300 seconds) is routinely computed (and corrected) in each subject by the MCFLIRT program, part of FSL software package. Additionally, head motion time courses are also used in all first level analyses as a covariate of no interest (see methods for details), as a second step to further minimize its contribution to brain activity. The plot depicts the group average head motion as a function of time (lines correspond to the mean values and bars are standard errors, plotted every 25 seconds), in general deviations are smaller that 1 mm (smaller than the voxel size) during all functional scans. Bars represent the group average mean absolute displacement (i.e. average of time series). There were no significant differences across groups (unpaired t–test). **(b)** Top row shows example of three slices from a anatomical T1–weighted scan, from a subject used in the study. Bottom row depicts the masks used to compute gray matter SNR. SNR was computed by

dividing the mean signal from the gray matter tissue (green mask, identified using the FIRST segmentation tool in FSL) by the standerd deviation of the background noise (red mask). **(d)** Plot shows longitudinal changes in gray matter SNR for the three groups computed seperately using a repeated measure ANOVA. There were no differences for all groups. **(e)** Cross sectional differences in neocortical gray matter SNR for the three groups for visits 1, 2, 3 and 4. Groups differences were assessed using a 1–way Factorial ANOVA. There was no differences in gray matter SNR across groups for any visit. **(f)** Table showing the correlation between mean absolute displacement and functional connectivity parameters for all subject groups and visits. Except for NAc negative links at visit 4 in SBPr, functional connectivity did not exhibit any signifecant dependence on head motion.

a



b

	Visit 1		Visit 4	
	SBPr R (p-value)	SBPp R (p-value)	SBPr R (p-value)	SBPp R (p-value)
Gray matter volume	-0.27(0.24)	-0.15 (0.53)	0.05 (0.80)	-0.06(0.81)
NAc gray matter density	0.08(0.72)	-0.14 (0.55)	0.08 (0.71)	0.09(0.70)
putamen GM density	0.03(0.89)	-0.11 (0.63)	-0.27 (0.24)	0.24(0.35)
Caudate gray matter density	0.14(0.55)	-0.14 (0.55)	0.19 (0.40)	0.11(0.65)
insula gray matter density	0.03(0.89)	-0.31 (0.19)	-0.27 (0.24)	0.24(0.35)
S1/M1 gray matter density	-0.32(0.16)	0.11 0.64)	-0.05 (0.81)	-0.24(0.33)
MTG gray matter density	0.12(0.60)	-0.35 (0.13)	-0.05 (0.81)	-0.24(0.33)
NAc positive links	-0.32(0.16)	-0.12 (0.61)	-0.03 (0.88)	-0.18(0.48)
NAc negative links	-0.21(0.37)	-0.27 (0.25)	-0.30 (0.19)	-0.14(0.56)
insula positive links	0.25(0.28)	-0.34 (0.17)	0.03 (0.88)	0.15(0.54)
insula negative links	-0.02(0.93)	-0.30 (0.21)	-0.02 (0.93)	0.33(0.19)
S1/M1 positive links	-0.06(0.79)	-0.27 (0.25)	-0.09 (0.69)	-0.38(0.13)
S1/M1 negative links	-0.18(0.43)	0.06 0.81)	0.13 (0.57)	-0.12(0.64)
NAc-mPFC *z(r)*	-0.08(0.72)	-0.15 (0.53)	-0.30 (0.19)	-0.15(0.56)

Supplementary Figure 9. Medication usage for SBP

(a) Plot shows the mean ± S.E.M. scores on the medication quantification scale (MQS) for SBPp and SBPr over the period of study. MQS scores were relatively low and did not exhibit any changes in time (repeated measures ANOVA) or between groups across all visits (two–sided unpaired t–test). **(b)** Table shows the association of medication usage with global gray matter volume, local gray matter density and functional connectivity measurements for SBPr and SBPp at visits 1 and 4. MQS did not exhibit any significant relationship to all measures assessed in the study. MQS is a validated pain medication use questionnaire, which generates equivalences between various analgesic drugs.

	Healthy	SBP	SBP (validation)
Number of subjects	17	39	13
Age	37.7 ±1.8	40.9 ±2.3	42.3 ±2.9
Gender	7 females (41.2%)	20 females (51.2%)	6 females (46.2%)
Education (years)	14.8±1.8	15.1±0.5	13.8±0.6

Supplementary Table 1. Demographic parameters for healthy subjects and SBP patients. Patients and healthy were matched for age, gender and education. Data presented as Mean±SEM

	Visit 1			Visit 4		
	SBPp (Mean±SEM)	SBPr (Mean±SEM)	SBPp>SBPr (t–score)	SBPp (Mean±SEM)	SBPr (Mean±SEM)	SBPp>SBPr (t–score)
VAS (0–100)	54.1±5.0	51.4±4.2	0.42	58.9±5.1	17.2±3.4 ↓	6.73**
MPQ *sensory*	11.9±1.7	9.2±0.9	1.42	13.3±1.3	4.8±1.2 ↓	4.50**
MPQ *affective*	3.3±0.6	1.6±0.4	2.09*	3.5±0.8	0.9±0.4 ↓	2.66*
MPQ *radiulopathy*	5.2±0.5	4.1±0.4	0.46	5.2±0.6	3.9±0.4	2.65*
NPS	38.6±5.1	36.2±2.6	1.34	44.9±2.1 ↑	14.2±1.9 ↓	5.91**
BDI	6.4±1.0	6.7±1.3	–0.83	9.3±2.1	3.8±0.8 ↓	2.02
PANAS *positive*	33.4±1.7	29.1±2.5	1.41	32.5±1.7	35.4±1.6	1.17
PANAS *negative*	22.5±2.6	22.7±3.1	–0.05	20.4±1.7	14.4±1.1 ↓	2.89**

Supplementary Table 2A. Pain and mood parameter differences between SBPp and SBPr. Clinical pain and mood parameters for SBPp (n=19) and SBPr (n=20) at visit 1 and visit 4. Significant changes between visit 1 and visit 4 (paired t–test, $p<0.01$) are displayed as increases (↑), or decreases (↓). VAS=visual analogue scale; MPQ = McGill pain questionnaire; NPS = Neuropathic pain scale; BDI = Beck's depression index. PANAS = Positive Affect Negative Affect Scale. [*$p<0.05$ **$p<0.01$, unpaired t–test]

	Visit 1			Visit 4		
	SBPp (Mean±SEM)	SBPr (Mean±SEM)	SBPp>SBPr (t–score)	SBPp (Mean±SEM)	SBPr (Mean±SEM)	SBPp>SBPr (t–score)
VAS (0–100)	65.1±5.3	57.8±9.2	0.75	58.4±10.1	21.3±9.3 ↓	–2.64*****
MPQ *sensory*	15.0±2.9	12.5±2.1	0.67	9.9±3.4	5.2±1.4 ↓	–1.20
MPQ *affective*	3.6±1.4	3.1±1.3	0.24	3.4±1.0	1.3±0.8	–1.57
MPQ *radiulopathy*	4.8±0.8	5.2±0.7	–0.27	4.3±0.9	2.6±0.6	–1.12
NPS	49.8±6.1	44.3±6.3	0.61	33.2±6.8	14.5±5.3 ↓	–2.10
BDI	6.3±1.9	6.7±1.9	–0.12	4.0±1.7	4.7±2.4	0.22
PANAS *positive*	31.4±2.2	33.6±1.5	–0.78	31.7±3.4	32.7±3.5	0.19
PANAS *negative*	22.3±3.1	17.0±2.1	1.35	17.0±2.3	17.0±2.4	0.00

Supplementary Table 2B. Pain and mood parameter differences between SBPp and SBPr for the validation group

Clinical pain and mood parameters for SBPp (n=7) and SBPr (n=6) at visit 1 and visit 4. Significant changes between visit 1 and visit 4 (paired t–test, $p<0.01$) are displayed as increases (↑), or decreases (↓). VAS=visual analogue scale; MPQ = McGill pain questionnaire; NPS = Neuropathic pain scale; BDI = Beck's depression index. PANAS = Positive Affect Negative Affect Scale. [*$p<0.05$ **$p<0.01$, unpaired t–test] Data presented as Mean±SEM.

Group	Brain region	Coordinates			F–zstat
		x	y	z	
Healthy	right STG	42	–30	8	4.29
	right LOC	48	–74	–10	4.21
	right MTG	58	–58	2	4.11
SBPr	right LOC	46	–76	–10	3.32
	right MTG	56	–58	2	2.59
SBPp	right NAc	10	12	–8	3.61
	right putamen	22	8	–6	3.52
	right caudate	12	12	6	3.48
	right insula	40	–6	–2	3.15
	left putamen	–24	–6	–4	3.01
	left insula	–38	–6	0	2.57
	left caudate	–10	12	0	2.42
	left NAc	–10	8	–10	2.31
	left M1	–32	–20	68	4.01
	left S1	–32	–34	66	4.11
	left ITG	42	–42	–18	3.32
	right MTG	52	–60	2	2.61

Supplementary Table 3. Coordinates of peak foci for whole brain longitudinal ANOVA for gray matter density

Talairach x, y, z coordinates in mm. M1 = primary motor cortex; S1 = primary sensory cortex; NAc = nucleus accumbens; ITG = Inferior temporal gyrus; MTG = middle temporal gyrus; LOC = lateral occipital cortex; MTG = middle temporal gyrus.

Parameter	Odds Ratio	Standard Error	Z–score	p–value	95 % Confidence Intervals
mPFC–NAc z*(r)*	4.52	2.79	2.45	0.01	1.35 – 15.13
VAS	1.08	0.36	0.25	0.80	0.59 – 1.98
Duration	2.19	0.81	2.13	0.03	1.06 – 4.52
MPQ sensory	1.87	0.64	1.83	0.07	0.97 – 3.63
MPQ affective	1.44	0.47	1.11	0.27	0.76 – 2.71
MPQ radiculopathy	1.22	0.36	0.62	0.53	0.66 –2.26
NPS	1.19	0.37	0.56	0.57	0.65 – 2.19
BDI	1.09	0.33	0.28	0.78	0.60 – 1.97
PANAS positive	0.66	0.21	–1.27	0.20	0.35 –1.25
PANAS negative	1.58	0.53	1.36	0.17	0.82 – 3.04
Early drug use	0.19	0.22	–1.45	0.15	0.02–1.81

Supplementary Table 4A. Odds ratio for predicting SBPp and SBPr groups at visit 4 based on brain, pain and drug use parameters measured at visit 1

Odds ratios and statistical significance are shown for functional connectivity of NAc–mPFC, pain and mood parameters, and for early drug use. All parameters except early drug use were converted to quartiles to make the odds ratios directly comparable. Early drug use was a binary parameter, defined as use of medication for pain relief at time of entry into the study. Functional connectivity and pain duration were significant separate predictors of pain chronification while MPQ sensory was borderline significant.

Parameter	Odds Ratio	Standard Error	Z–score	p–value	95 % Confidence Intervals
NAc – mPFC z*(r)*	7.14	5.85	2.40	0.02	1.43 – 35.63
MPQ sensory	3.67	2.04	2.34	0.02	1.23 – 10.94
Early drug usage	0.04	0.06	–2.08	0.04	0.01 – 0.83

Supplementary Table 4B. Multiple logistic regression model for predicting SBPp and SBPr groups at visit 4

The model shows that all three parameters significantly contribute to predicting pain chronification. The resultant model chi–square(df=3)= 18.3 with p–value = 0.0004, with a discrimination D–value=0.88. In comparison D–values for separate predictors for NAc–mPFC, MPQ sensory and early drug use were: D=0.76, 0.69, and 0.61. When all four D–values are contrasted we observe that the multiple regression model is superior to each of the separate predictors, chi–square (df=3)= 27.0, p–value<0.00005. We also tested adding duration as an additional independent parameter, to the model. Although duration is a signficant predictor by itself, it becomes non–significant in the multiple regression model.