These results demonstrate a strong association between smoking at the time of the onset of back pain symptoms for longer term pain chronification. This clinical outcome was established by searching through multiple clinical parameters, and was not a primary hypothesis of the study. Therefore, we label the observed result as an association that needs to be validated in a systematic study.

Strong association between smoking and transition from acute to chronic back pain

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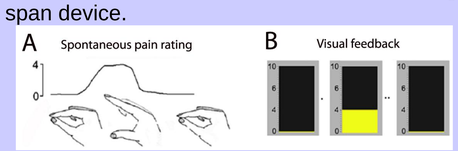
INTRODUCTION

- Mechanisms mediating the transition from acute to chronic pain remain largely unknown.
- In a longitudinal brain imaging study we followed over a one-year period subjects with a single episode of sub-acute back pain (SBP) as they either recovered (SBPr) or persisted into chronicity (SBPp), contrasted brain properties, and compared them to chronic back pain (CBP) and healthy controls.
- We previously showed that in SBPp there are region specific decreases in grey matter density, and increased functional connectivity that robustly predicts pain chronification (Baliki et al., 2012).
- Here we investigate the behavioral biomarkers that may also be predictive of pain chronification.

METHODS

- The study followed patients with subacute (SBP) back pain (< 3 mo duration, no back pain for at least a year prior to symptom onset), chronic back pain patients (CBP, pain >5 years), and healthy controls (CON) for 6 visits, over the course of one year.
- At each time point, patients completed behavioral questionnaires (including demographics, McGill Pain Questionnaire sensory and affective subscales, PainDETECT, and medication use), and were scanned at 2 weeks after recruitment, 6 weeks, 6 months and 1 year follow-up visits.
- Pain intensity measures were collected at each visit using the Visual Analogue Scale (VAS, 0-100), in which patients continuously rated their spontaneous back pain for 10 minutes in the scanner using a finger span device.



- Brain functional data was analyzed with FSL v4.1.8, to identify brain connectivity differences of the nucleus accumbens (NAc). Anatomical, T1 and DTI, data was also studied (see 181.18).
- Based on VAS scores, the SBP group was divided into persisting (SBPp) and recovering (SBPr) groups using a greater than 20% change in pain criterion, from visit 2 (scan 1) to visit 5 one year later. This segregation yielded 31 SBPr (age 42.77±0.39) and 37 SBPp (age 43.86±0.26) patients.

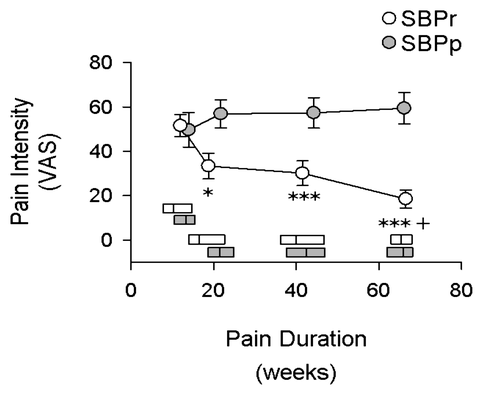
1 Longitudinal Study Design

	SBP	CBP	CON
Visit 1 - Baseline	160 37 withdrawals	3 24 withdrawals	35 6 withdrawals
Visit 2 - Scan 1	123 34 withdrawals	28 2 withdrawals	29 6 withdrawals
Visit 3 - Scan 2	89 13 withdrawals	26 2 withdrawals	24 1 withdrawal
Visit 4 - Scan 3	75	24	22
Visit 5 - Scan 4	68(pending 4)	24	22

Sample Demographic Summary

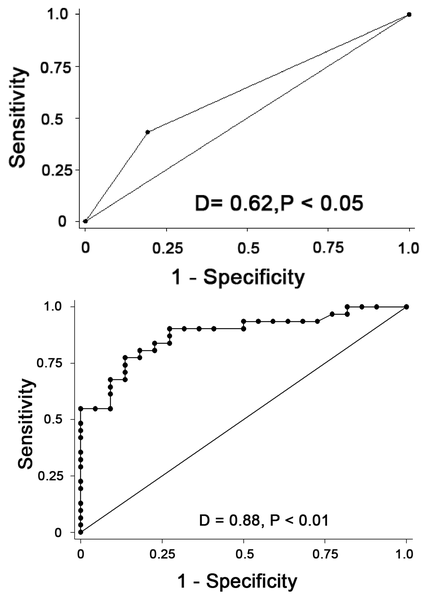
	SBPp	SBPr
Number	37	31
Gender		
Male	18	18
Female	19	13
Smoking Status		
Smoker on baseline visit	16	6
Non-smoker at baseline visit	21	25
Age (mean ± SD)	43.86±0.26	42.77±0.39

2 SBPr and SBPp pain ratings significantly differ within weeks of pain onset and persist 1 year later



- SBPr patients (n=31) reported decreases in VAS pain over the course of the study, and they significantly differed from SBPp patients (n=37) over a year. Horizontal bars show the median and inter-quartile range of pain durations for each group.
- A significant groupxtime effect (rm-ANOVA, $p<10^{-5}$) was identified. Post-hoc (Tukey) tests: $+p<0.05$ within group comparison to visit 1; $*p< 0.05$, $***p< 0.001$ group contrast at fixed time.

3 Smoking status predicts pain chronicity based on logistic regression models



a) Smoking status at time of entry into the study was the strongest predictor of SBPr and SBPp groups at one year from symptom onset, odds ratio =3.17, p<0.04, Confidence Interval, CI = 1.05-9.56, accuracy = 0.62.

b) MQS, MPQ-A and PainDetect were entered into a multiple regression logistic model. Inclusion of all four parameters revealed that smoking status remained the strongest significant predictor, with odds ratio = 6.65, p<0.022, CI = 1.31-33.70, Accuracy =0.88.

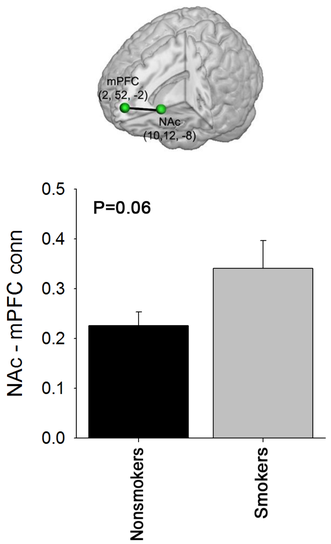
4 Final multiple logistic regression model predicting the chronicity of pain

Number of obs = 53
Area under ROC curve = **0.8776**

LR Chi^2(4) = 26.36
Pseudo R^2 = 0.3664
Prob > Chi^2 = 0.0000

Grouping	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf. Interval]	
Smoking	6.65	5.51	2.29	0.02	1.31	33.70
MPQa	1.88	0.74	1.59	0.11	0.86	4.09
pdetect	2.40	1.02	2.06	0.04	1.04	5.52
MQS	0.34	0.14	-2.65	0.01	0.15	0.76

5 Increased Nac-mPFC functional connectivity, predicting pain Chronification, is also increased in smokers



a) NAc functional connectivity was compared between SBPp and SBPr, revealing differences in connectivity to mPFC. Connectivity was increased in patients who had persisting pain (Baliki et al 2012).
b) T-test comparing the Nac-mPFC connectivity at scan 1 during the spontaneous pain rating task of smokers and nonsmokers. The result is borderline significant, with t= 1.906 p<0.065

CONCLUSION

- These novel results suggest that **smoking status at the time of pain onset may predict pain persistence**
- As smokers exhibited increased NAc-mPFC connectivity, and the latter predicts pain chronification, **we conclude that smoking influence is reflective of addictive behavior** rather than cholinergic activity.
- The serendipitous discovery of a behavioral correlate of the brain circuitry that is **critically implicated in the transition to chronic pain** demands systematic validation in an independent cohorts of subacute back pain patients.

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