Neurobiological Mechanisms Underlying Effectiveness of CBT in IBS patients – Lessons from Psychiatry

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Overview

- Why are we interested in brain correlates of CBT?
- Neurobiology of CBT effects in chronic pain
  - What are the abnormalities in IBS patients that may be targets for CBT?
  - Published evidence for neurobiological effects of CBT in chronic pain
- Neurobiology of CBT effects in psychiatric conditions
- The future:
  - Neurobiological correlates of CBT effects in IBS patients
  - Brain signatures as biomarkers and outcome predictors
Why are we interested in brain correlates of CBT?

- Cognitive behavioral treatment strategies (including hypnosis) are effective therapies for persistent pain disorder as well as disorders of mood and affect\(^1,2\)

- However, moderators (predictors) and neurobiological mediators of CBT effects in chronic pain conditions (as well as in mood and affect disorders) are largely unknown

- A better knowledge of these factors would help to identify responders, to better understand the pathophysiology of chronic pain mechanisms, and to optimize treatment strategies

1 Hofmann et al, 2012; 2 Naliboff et al, 2010; 3
CBT Effects on Clinical Global Improvement and Adequate Relief of GI Symptoms

Lackner et al., 2008.
Why are we interested in brain correlates of CBT?

- Cognitive behavioral therapy is an evidence based psychotherapeutic method, rooted in behaviorism and cognitive psychological theory.
- According to CBT theory, patients respond more to the cognitive representations and learned emotional memories of events, instead of responding to the events themselves.
- CBT treatments target maladaptive cognitions (error predictions), behavior patterns (avoidance behaviors) and associated emotional arousal.¹
Worrying About Pain: Prediction Error About Expected Interoceptive State

“I am worried this pain will be unbearable”
Brain Correlates of Prediction Error in IBS: Exaggerated Responses to EXPECTATION of Aversive Visceral Distension

Healthy control (n=18)
Activation of right anterior INS
Deactivation of pACC

Normosensitive IBS (n=18)
Activation of bilateral ant and post INS

Hypersensitive IBS (n=15)
Activation of bilateral INS, THAL

Larsson, et al, Gastroenterology 2012
Similar Enhanced Brain Responses to Expected and Delivered Aversive Visceral Distension in IBS

Healthy control  Normosensitive IBS  Hypersensitive IBS

Conclusion: Almost the entire group difference in brain response to rectal distension is explained by the group difference in pain expectation

Larsson et al, Gastroenterology 2012

Expectation

Distension (45 mmHg)
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¹ Lackner et al, 2010
The Biological Architecture of Symptoms in Persistent Pain Disorders

Processing of visceral signals within visceral brain axis

Physiological and pathophysiologic visceral signals
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Generation of conscious “gut feeling” from biol. signal

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Encoding of memory of feeling state (pain) and context

Recall of memory in response to internal and external cues

Physiological and pathophysiological visceral signals
Brain responses to acute visceral nociceptive stimuli

Subjective experience of visceral pain

Cognitive modulation

Sensory processing

Emotional arousal

Descending modulation

Tillisch, Labus, Mayer et al. 2010
Altered Cognitive Function in IBS: Potential target for CBT

- Altered engagement of prefrontal cortex during error feedback in IBS patients. *Aizawa, Fukudo et al., Gastroenterology 2012*

- Altered brain response to cued pain expectation in IBS. *Berman et al. J. Neurosci 2008;*

- Cued expectation of aversive visceral distension is associated with increased engagement of insula cortex. *Larsson et al. Gastroenterology 2012*
Emotional arousal circuits: Potential target for CBT

In female IBS during pain expectation, and during distension  *Labus et al. 2008*

In female control subjects during ATD  *Van Nieuwenhoven, Mayer et al. Gut 2011*

Normalization of altered connectivity in IBS by CRF-R1 antagonist  *Hubbard et al, J Neurosci 2011*

and by NK1 receptor antagonist  *Tillisch et al, APT 2011*

Evidence for alterations in central noradrenergic systems in IBS  *Berman et al. J. Neurosci 2008;  Berman et al. Neuroimage 2012*
Do Cognitive Behavioral Therapies Change the Brain in Persistent Pain Conditions?

• To date, published studies on the effect of non-pharmacological pain treatments on the brain have not been conclusive and methods have been suboptimal⁴
• However, several of these therapies were associated with increased pain related activations of prefrontal regions (ventro and dorsolateral PFC) and decreased activations in sensory processing and affective brain regions⁴
• Despite the demonstrated effectiveness of CBT for various chronic pain conditions, only 3 controlled trials²-³ have been published evaluating the brain correlates of effective therapy

¹ Jensen et al. 2012; 2 Lackner et al. 2006; Jensen et al. 2012; Lowen et al 2013
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Cognitive Behavioral Therapy increases pain-evoked activation of the prefrontal cortex in patients with fibromyalgia

Karin B. Jensen\textsuperscript{a,b,*}, Eva Kosek\textsuperscript{c,d}, Rikard Wicksell\textsuperscript{c,e}, Mike Kemani\textsuperscript{c,e}, Gunnar Olsson\textsuperscript{e,f}, Julia V. Merle\textsuperscript{g}, Diana Kadetoff\textsuperscript{c,d}, Martin Ingvar\textsuperscript{c,d}

METHODS:
• RTC in 43 women with FM comparing 12 week CBT with wait list control
• Pressure pain evoked brain responses with fMRI
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RESULTS:
• In CBT group larger symptomatic improvement
• No change in experimental pain perception
• Increased activation of ventro- and dorsolateral brain regions
• Increased functional connectivity between vl PFC and thalamus
Effect of hypnotherapy and educational intervention on brain response to visceral stimulus in the irritable bowel syndrome

M. B. O. Löwen*†, E. A. Mayer‡, M. Sjöberg§, K. Tillisch†, B. Naliboff¶, J. Labus¶, P. Lundberg++††‡‡§§, M. Ström++++, M. Engström*** & S. A. Walter*

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• fMRI responses to evoked visceral pain and its expectation
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## Does Cognitive Behavioral Therapy Change the Brain in Anxiety Disorders?

<table>
<thead>
<tr>
<th>Study</th>
<th>Mental Disorder</th>
<th>Neuroimaging Technique</th>
<th>Neuroimaging Findings</th>
</tr>
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<tbody>
<tr>
<td>Paquette et al. (2003)</td>
<td>Spider phobia</td>
<td>fMRI</td>
<td>After CBT there was significant activation of the dorsolateral prefrontal cortex and parahippocampal gyrus regions.</td>
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<td>Straube et al. (2006)</td>
<td>Spider phobia</td>
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<td>After treatment the CBT group displayed absence of activation of the anterior ventral insula and failed to show any difference from the healthy control subjects.</td>
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<td>Fumark et al. (2002)</td>
<td>Social phobia</td>
<td>PET</td>
<td>After treatment with CBT and citalopram, there was reduction of activities at the temporal lobe regions, mainly at the right hemisphere. Decreased activity at the right amygdala, hippocampus, rhinal activity, and periamygdaloid.</td>
</tr>
<tr>
<td>Farrow et al. (2005)</td>
<td>PTSD</td>
<td>fMRI</td>
<td>In the social cognition of empathy there was significant activation of the left posterior and anterior medial temporal gyrus and posterior cingulate gyrus. As for the forgiveness-related cognition, there was activation of the posterior cingulate, medial frontal gyrus, posterior cingulate activation, medial frontal gyrus, and left posterior medial temporal gyrus.</td>
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<td>Baxter et al. (1992)</td>
<td>OCD</td>
<td>PET</td>
<td>After treatment the CBT and medication groups showed decreased activation of the head of the right caudate nucleus.</td>
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<td>Schwartz et al. (1996)</td>
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<td>PET</td>
<td>After treatment the patients presented significant decrease of activation of the right caudate nucleus. When the subjects of this study were combined with those of the previous study (Baxter et al., 1992), they showed as well reduced activation of the left caudate nucleus.</td>
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<td>Brody et al. (1998)</td>
<td>OCD</td>
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<td>The higher metabolism of the left frontal orbital cortex before treatment was associated with a better response to BT.</td>
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<td>Nakao et al. (2005)</td>
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<td>After treatment there was a decrease in the activation of the frontal orbital cortex.</td>
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<td>Prasko et al. (2004)</td>
<td>Panic</td>
<td>PET</td>
<td>The increase of activity in the left hemisphere was mainly in the prefrontal, temporoparietal and occipital regions. In the right hemisphere, in the posterior cingulate. The decrease was predominant at the left hemisphere in the frontal region, and at the right hemisphere in the frontal, temporal, and parietal region.</td>
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<td>Sakai et al. (2006)</td>
<td>Panic</td>
<td>PET</td>
<td>After treatment there was decrease in the metabolism at the right hippocampus, left ventral anterior cingulate cortex, uvula, and pyramid of the left cerebellum and pons. The increased metabolism was found in the bilateral medial prefrontal region.</td>
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fMRI = functional magnetic resonance imaging; PET = positron emission tomography; CBT = cognitive behavior therapy; PTSD = posttraumatic stress disorder; OCD = obsessive-compulsive disorder

Does Cognitive Behavioral Therapy Change the Brain in Psychiatric Disorders

- Cognitive behavioral therapy modified neural circuits involved in the regulation of negative emotions and fear extinction in treatment responders, including prefrontal regions, anterior insula, cingulate subregions and hippocampus
- The only study on predictors of response (OCD) showed higher pretreatment metabolic activity in left orbitofrontal cortex associated with a better response to treatment
- Significant methodological limitations include small sample size, lack of placebo control conditions, and different treatment strategies

Modulation of Cortical-Limbic Pathways in Major Depression

- Similarities and differences in changes in brain changes in regional glucose metabolism between CBT and paroxetine were observed.
- In CBT, decreased brain metabolism in frontal and parietal regions, and increases in hippocampus and ACC were observed.
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Does Cognitive Behavioral Therapy Change the Brain? A Systematic Review of Neuroimaging in Anxiety Disorders

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Summary

- Considering the effectiveness of cognitive behavioral therapies for the treatment of chronic pain conditions, it is surprising how few studies have addressed the neurobiological mechanisms underlying its clinical effectiveness.
- Limited data suggest normalization of altered cortico-limbic-pontine interactions
Hypothesized Effects of CBT on Impaired Cortico-limbic-pontine networks in Persistent Pain and Affective Disorders

Impaired cortico limbic inhibition

Normalized cortico limbic inhibition

mPFC
pACC
vlPFC
dIPFC

PAG

Dorsal ANTERIOR INSULA ventral

dorsal ANTERIOR INSULA ventral

Affective circuits

After CBT
Questions for the Future

- Which type of chronic pain syndrome responds best to CBT as opposed to pharmacotherapy?
- Are there subgroup of patients within a particular syndrome that respond best to CBT?
- Is one type of CBT more effective than others?
- How sustained is the effect?
- Are functional improvements associated with reversal of structural changes?
- Can brain signatures from multimodal brain imaging studies be used as biomarkers to monitor therapeutic effects of CBT?
- Can such biomarkers be used as predictors of outcome?
Ongoing Studies

Neuroimaging biomarkers of Mind-Body treatment response in chronic visceral pain
1R01AT007137  Tillisch/Naliboff (co-PIs)
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**Neuroimaging biomarkers of Mind-Body treatment response in chronic visceral pain**  
1R01AT007137  Tillisch/Naliboff (co-PIs)

**Neurobiological mechanisms underlying effectiveness of CBT in IBS patients**  
R01 DK096606  Mayer/Lackner (co-PI’s)

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Development of a brain image repository to facilitate identification of brain signatures/biomarkers to be used in future clinical trials of CBT and other therapies (PAIN.loni.ucla.edu)
CNS

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uclacns.org
pain.loni.ucla.edu
pain.loni.ucla.edu

- Provide infrastructure for storage and sharing of functional and structural brain imaging data and associated metadata from multiple scanning sites
- Provide tools for QC and analysis of the resulting comprehensive data sets
- Facilitate new discoveries in brain endophenotypes and biomarkers of chronic pain states