What neurobiology teaches us about NSSI and why this knowledge helps in clinical practice

Univ. Prof. Dr. Paul Plener, MHBA

Outline

• Emotion regulation and pain
• Stress response and reward
• Social stress
• Model
• Therapy
• Discussion
MB23.E Non-suicidal self-injury

- Intentional self-inflicted injury to the body, most commonly cutting, scraping, burning, biting, or hitting, with the expectation that the injury will lead to only minor physical harm.


Biopsychosocial model
Emotion regulation and pain

Results: all pictures

NSSI: More activity in Amygdala bilaterally for all stimuli

NSSI: More activity in ACC for all stimuli

NSSI: More activity in Orbitofrontal Cortex when watching NSSI pics

Plener et al., 2012
**Analgesia in adults**

- BPD+NSSI ~ 80%: hypalgesia to analgesia

- Pain threshold elevated in BPD+NSSI
  - mechanical
  - chemical
  - electrical
  - temperature (hot/cold)
  - electromagnetic

- Hypalgesia is habitual:
  - Pain threshold decreases after stopping NSSI

Bohus et al., 2000, Cardenas-Morales et al., 2011, Schmahl et al., 2004, 2006, Ludäscher et al., 2009, Reitz et al., 2015

---

**Pain works in BPD**

Higher activity in the DLPFC and deactivation of the ACC and amygdala

Pronounced reduction of amygdala activation after incision (compared to sham condition): additive effect of tissue damage and of seeing blood

Functional connectivity: painful stimuli:
- enhanced negative coupling between (para-)limbic and prefrontal structures: inhibition of limbic arousal
- enhanced connectivity between DLPFC and posterior insula: altered, positive appraisal of pain

Schmahl et al., 2006; Kraus et al., 2009; Schmahl & Baumgärtner, 2015; Reitz et al., 2015; Niedtfeld et al., 2012
**Pain processing**

- Thermal grill illusion: hot and cold stimuli simultaneously
- Illusionary pain: no nociceptive input, but perceived painful through central integration of thermoafferent signals
- Higher pain thresholds in current BPD, less unpleasant
- Ability to perceive illusion is intact
- Sensory-discriminative properties unaffected: uncoupling of aversive evaluation and sensory perception

---

**Pain processing**

- N=30 females (mean age: 22.4, SD=3.37)
- 14 with lifetime history of NSSI (DSM-5 at least for one year in past eight years): former patients of Dept. of CAP
- 6 of them with NSSI within the last year
- All of them with history of skin-cutting
- 16 HCs: no history of psychiatric or neurological disorders, no NSSI

- Scans during follicular phase
- Unpleasant electric stimulation: 4 levels of intensity
- Individual upper and lower boundaries of stimulus intensity
Pain processing

- Both groups: increasing activation of posterior insula activity and somatosensory cortex:
  - Differences in left middle insula
  - Only in HC: increasing activity in anterior insula

Bonenberger et al., 2015

Pain processing

- No differences in numbers of correct subjective rating of stimulus intensity
- No differences in posterior insula and primary somatosensory cortex: intact discriminant perception
- Changes in activation of anterior insula:
  - processing affective aspects of pain
  - responds to arousal and attention
  - involved in processing of emotional states and emotional regulation
  - higher activation: anticipation of potentially damaging stimuli

Bonenberger et al., 2015; Zaki et al., 2016; Wiech et al., 2010
Emotion dysregulation and diminished pain perception

- Adults with (n=25) or without (n=47) NSSI
- CPT: pain threshold, pain tolerance

Emotion dysregulation: mediates pain tolerance in NSSI

Pain & NSSI in adolescents and young adults

- Participants aged 16-24 (n=13 NSSI, 15 nonNSSI)
- Cold and cool stimuli self- or experimenter administered
- No differences in pain ratings & activation during pain
- Decreased functional connectivity OFC-ACC
- Higher ratings of relief in NSSI group
- Differences in activation in i.e. dorsal striatum, thalamus, precuneus, posterior cingulate cortex during relief: reward system, processing pain

Franklin et al., 2012
Osuch et al., 2014
Pain offset relief

- “Painful, negative events…worth remembering: what made them happen and what made them cease?”
- Mechanisms in Drosophila, Rats and Humans
- Insula involved in pain offset

Pain offset relief in NSSI

- Pain offset relief decreases negative affect and increases positive affect at the same time
- Positive affect: startle postauricular activity, negative affect: startle eyeblink reactivity (heightened by unpleasant stimuli)
- N=42 (21 with NSSI, 21 HC): painful electrical shocks; NSSI: at least one episode of NSSI: range: 1-3000
- No correlations between frequency of NSSI and pain offset relief
- NSSI group: Reduction of eyeblink reactivity at 6s: not significant after controlling for emotional reactivity
Endogenous opioids

- Play a role in various disorders with NSSI and self-mutilation (BPD, PDD,...); Opioid antagonist somewhat successful in treating self-injury in PDD
- Involved in pain perception (different opioids play different roles)
- Opioids with affinity for µ receptors: Self administered: hedonic properties of reward
- Deficit due to childhood stress
- CSF levels: 29 BPD & Cluster B PD (14 with NSSI, 15 no NSSI, all SA)
  - β-endorphin and met-enkephalin (µ- & delta receptor agonists)
  - No difference:
    - Homovanillic acid (dopamin metabolite)
    - 5-HIAA (serotonin metabolite)
    - Dynorphin

Neurobiological model of NSSI

Adverse Childhood Experiences
Genetic Influences

HPA Axis Abnormalities
Endogenous Opioid Abnormalities
Serotonergic Abnormalities
Dopaminergic Abnormalities

Stress Vulnerability ↑

Stress
Altered Opioid Homeostasis

NSSI
Homeostasis restored

Sher & Stanley, 2008, 2009; Bresin & Gordon, 2013; Stanley, 2010

Sher & Stanley, 2009
Summary of altered pain mechanisms

- Pain
- Stress/inner tension
- (Self-) Injury

Conclusions: emotion regulation

• Within regions responsible for emotional processing a former hyper-activation in individuals with NSSI can be countered by the injury
• NSSI serves an active role in emotion regulation by influencing areas in the brain involved with emotion processing.
• The notion of patients that NSSI “works” to alleviate strong negative emotions is supported by replicated evidence from fMRI studies.
• The potential barrier of pain plays no significant role
Stress response and reward

NSSI works for stress

NSSI is primarily used to regulate stress and emotions

- while imaging emotional and cognitive reactions to a stressful situation
  - Decrease of activation in the left OFC (failure to inhibit emotional reaction?)
  - Increase in the DLPFC (also in abuse scripts)

- While imaging NSSI:
  - Decrease in the posterior ACC (deficits in active monitoring; enhanced emotional involvement)

Taylor et al., 2018; Kraus et al., 2010
Deficient emotion regulation

• N=48, all f, mean age: 28.0 (SD: 4.2), 21 with DSH, matched for demographics, depression and anxiety
• Neutral and negative IAPS images
• Negative images: LOOK:CHANGE (reappraisal)
• Controls: successful decrease in bilateral amygdala activation during reappraisal
• NOT in DSH group: greater activation in amygdala, MPFC and PCC
• Poor ability to down regulate negative emotions

Davis et al., 2014

Cognitive interference

• Young adults (NSSI: 15; HC: 15)
• Multi-Source Interference Task
  • Activation of cingulo-frontal-parietal attentional network
  • No differences in task performance
  • NSSI: cingulate cortex↑; DLPFC ↓
• DLPFC ↓:
  • poorer emotional control
  • increased impulsivity

Dahlgren et al., 2018
**Reward-related neural activation**

- fMRI study (n=71, 12-14y) adolescents with thoughts on NSSI
- Monetary incentive
- Increased activation in the putamen
- Heightened sensitivity to reward
- Linked to endogenous opioids?
- Heightened reward sensitivity: risk behavior prone?

![Image of bilateral putamen with reward-related neural activation graphs]

**Monetary incentives: rewards**

- Adolescents (NSSI: 19, HC: 19; 13-19y)
- Monetary incentive delay task
- NSSI: during anticipation of reward
  - striatal and orbitofrontal cortex regions ↓
  - Bilateral amygdala activation ↓
- Limited hedonic value from ordinary rewards: seek other rewards?

![Image of brain regions with monetary incentives reward graphs]
Reward in the EEG

- N=57, 7-11y (NSSI: 19)
- NSSI: larger responses to losses than to gains (delta in feedback negativity gains vs. losses)
- After controlling for psychopathology

![Graph showing reward in the EEG]

Conclusion: stress response

- individuals with NSSI seem to be prone to an elevated stress reactivity.
Social stress

Results: valence and activity

Less activity in BA 45 R * the higher the valence in NSSI group compared to controls

* Rizzolatti et al., 1996  Plener et al., 2012
Emotion recognition intact?

- CAP inpatients with SA (30), NSSI (30) & HC (30): 13-17 years
- NSSI vs. HC: more errors in recognizing fear in child and sadness in adult faces

- Adolescents with NSSI (47), clinical CAP controls (28) & HC (51): 13-19 years
- No differences in emotion recognition
- Neutral & happy faces: lower valence in NSSI vs. HC
- Anger and sadness: higher arousal: NSSI vs. HC

Youth culture & NSSI

- **Alternative identity:**
  - Association with NSSI (r=0.20-0.24),
  - Frequency of NSSI (r=0.32-0.35)
  - Suicidal ideation (r=0.13-0.20)
  - Suicide attempts (r=0.25-0.29).

- **Athletic identity:**
  - Negatively associated with NSSI (r=-0.11-0.18)
Youth culture & NSSI

Risk of depression and self-harm in teenagers identifying with goth subculture: a longitudinal cohort study

ALSPAC study (n=3694):
Identifying as a goth at age 15 - risk of self-harm at age 18

No identification: 10%
Very much: 37%

<table>
<thead>
<tr>
<th>Self-harm</th>
<th>OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linear effect</td>
<td>537 3694</td>
<td>1.52 (1.42-1.63)</td>
</tr>
<tr>
<td>Not at all</td>
<td>2759 1841</td>
<td>Reference</td>
</tr>
<tr>
<td>Not very much</td>
<td>1234 884</td>
<td>1.52 (1.20-1.93)</td>
</tr>
<tr>
<td>Somewhat</td>
<td>716 523</td>
<td>2.33 (1.80-3.02)</td>
</tr>
<tr>
<td>More than somewhat</td>
<td>410 292</td>
<td>3.65 (2.72-4.89)</td>
</tr>
<tr>
<td>Very much</td>
<td>238 154</td>
<td>5.14 (3.58-7.36)</td>
</tr>
</tbody>
</table>

Youth culture & NSSI

Risk of depression and self-harm in teenagers identifying with goth subculture: a longitudinal cohort study

<table>
<thead>
<tr>
<th>Low goth self-identification</th>
<th>High goth self-identification</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Being bullied at age 8</td>
<td>39%</td>
<td>47%</td>
</tr>
<tr>
<td>Being bullied at age 15</td>
<td>12%</td>
<td>16%</td>
</tr>
</tbody>
</table>
Genes & NSSI: GxE interactions


Hankin et al., 2015

Bullying as risk factor for DSH & NSSI

- ALSPAC & GSMS: (n=4026 & 1420): Bullying predicts self-harm (differences not explained by poly-victimisation)

- German students (n=647, mage: 12.8)
  - Frequent bullying(≥ 2-3x in last three months):
  - OR for NSSI: 11.75

Lereya et al., 2015; Jantzer et al., 2015
HPA axis and NSSI

• Altered cortisol response after TSST

N=28, 16.6 years
Saliva Cortisol

N=224; NSSI: 21 (9.4%), f: 15
19 years
Cortisol levels in blood

Evoking social pain

• Social exclusion: “Cyberball”
  • 60 throws ‘passive’
  • 60 throws inclusion (1/3 randomized: receiving ball)
  • 10 throws inclusion, 50 throws exclusion
Sensitivity vs. social rejection

Social rejection „hurts“

- Exclusion > Inclusion: vlPFC und mPFC

Groschwitz et al., 2016

Peak-Voxel: -28 28 -12
p<.005

** p<.001
* p<.05

Peak-Voxel: 12 52 8
p<.005

Groschwitz et al., 2016

Mean scores of cluster, peak voxel at -28 28 -12
Activation vlPFC
Peak-Voxel:

Mean scores of cluster, peak voxel at 12 52 8
Activation mPFC (excl>incl)
**Social rejection „hurts“**

- Exclusion > Inclusion:
  - NSSI: higher activation in ventral striatum + hippocampus + mPFC + anterior insula
  - Social rejection more salient for adolescents with NSSI?

**OPRM1 and pain**

- Activation of the pain matrix in both physical and social pain is influenced by a polymorphism of a µ opioid receptor gene: OPRM1

- A118G polymorphism, AA and AG genotype:
  - Increased activation of secondary sensorimotor cortex in social pain
  - Increased activation of superior frontal gyrus and precentral gyrus in physical pain
  - Enhanced sensitivity to social rejection
Conclusion: social stress

• Especially when encountering social stressors:
  • altered response of the HPA-axis centrally involved in the stress response.
  • Dysfunctional response to social stressors possible

• Heightened sensitivity regarding social exclusion from groups: bullying as risk factor

Putting the pieces together
Putting it all together

Modulation by polymorp.

stress → Altered stress response → NSSI → Stress relief

Distorted perception

HPA axis

Endogen. opioids

Pain offset relief

What can we learn about therapy?
Therapy

• N=22, 11 HC vs. 11 BPD: DBT
• Down-regulation of dysregulated emotion and amygdala activity in BPD after DBT (12 month FU)

Goodman et al., 2014

New avenues: real time fMRI Neurofeedback

• Training of amygdala down-activation in response to negative visual stimuli
  • Works with HC
  • Specific for amygdala (vs. sham condition)
  • Leads to increased amygdala-ventromedial prefrontal cortex connectivity when regulating
  • Altered resting-state amygdala-lateral prefrontal cortex connectivity

Paret et al., 2014; Paret et al., 2016
New avenues: Online Therapy

Teenagers often face high barriers to treatment
Stress happens in everyday life
The need to get therapeutic intervention in daily life

Calm Harm: Winner of the Digital Innovation Award: National Positive Practice in Mental Health Awards 2016

Online Treatment program: in development

Discussion

• NSSI is a highly prevalent phenomenon in adolescence, often serving an affect regulation function

• Neurobiological research points to an altered processing of social and emotional stimuli

• NSSI works for decreasing stress

• Linking environmental to neurobiological conditions can help to foster our understanding of NSSI

• Treatment is available and working
Thank you for your attention!

paul.plener@meduniwien.ac.at