Neurocognition and Neuroimaging Correlates of Persistent Negative Symptoms

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NEGATIVE SYMPTOMS

**Anhedonia**
Loss of Pleasure

**Asociality**
Decreased Social Drive

**Avolition**
Lack of Motivation

**Blunted Affect**
Emotional Unresponsiveness

**Alogia**
Impoverished Speech

Kirkpatrick et al. 2006
WHAT IS THE IMPACT OF PERSISTENT NEGATIVE SYMPTOMS?

1. Contribute to poor functional and clinical outcome (Ho et al. 1998; Bodnar et al. 2008)

2. Related to elevated levels of treatment discontinuation (Galderisi et al. 2012)

3. Associated with cognitive deficits (O’Leary 2000)
WHY STUDY PNS IN FEP?

1. Avoid confounds due to illness chronicity
   - Antipsychotic medications
   - Sedentary lifestyle
   - Institutionalization

2. Identify them earlier and provide appropriate treatment
Functional Outcome in FEP

Background  Defining PNS  Memory and PNS  Neural Correlates of PNS  Conclusion
PERSISTENT NEGATIVE SYMPTOMS?

Include both primary and secondary negative symptoms

Identified using any validated negative symptoms scale (i.e. SANS, PANSS)

Estimated prevalence in FEP: 15-40%

Buchanan 2007; Malla et al. 2004
CRITERIA FOR PNS

Hовington et al. 2012; Buchanan 2007; Malla et al. 2004

Score ≥ 3 on SANS on a min of 1 global item of the SANS

Min. depressive + extrapyramidal symptoms

Have moderate NS at “initial baseline” (month 3)

At least moderate severity of NS

Min. positive symptoms

Maintain moderate NS for min of 6 months

PNS
Prevalence of PNS in FEP: 27%

Patients with PNS had poorer functional outcome (at month 12) compared to patients without PNS

Hovington et al. 2012
Functional Outcome in FEP

Cognitive

PNS

Biological

Background  Defining PNS  Memory and PNS  Neural Correlates of PNS  Conclusion
Patients with more severe NS = \downarrow neurocognitive performance

(Bora et al. 2009; McDowd et al. 2011; Puig et al. 2008)

1. Avolition correlated with verbal memory impairments
   (Brebion et al. 2000)

2. Alogia correlated with poorer working memory and verbal fluency
   (Berenbaum et al. 2008)
LONGITUDINAL RELATIONSHIP

- Most studies provide evidence for relative stability of cognition over time in FEP (Becker 2010; Bowie 2005)

- Others have shown that improvements in negative symptoms are paralleled with cognitive improvements (Censits 1997; Schuepbach 2002)

1) Investigate memory ability in FEP patients with PNS
2) Assess the trajectory of memory in relation to PNS over a 12 month period
METHODS
HOVINGTON ET AL. 2012

Visual Memory: Logical Memory (WMS-III)
Verbal Memory: Visual Reproduction (WMS-III)
Working Memory: Spatial and Digit Span (WAIS-III)

Change over time

Controls (62)
Non-PNS (97)
PNS (37)
Initial Assessment

Non-PNS (88)
PNS (34)
Month 12

Background  Defining PNS  Memory and PNS  Neural Correlates of PNS  Conclusion
RESULTS: MEMORY AND PNS

Greater levels of Alogia in PNS was correlated with poorer verbal memory.

* p<0.001
Functional Outcome in FEP

- Cognitive
- Biological
- PNS

Background  Defining PNS  Memory and PNS  Neural Correlates of PNS  Conclusion
A) Right medial frontal gyrus: decreased gray matter in PNS

B) Right parahippocampal gyrus: decreased gray matter in PNS

p<0.05, FWE-corrected

Benoit et al. 2012
Therefore, we investigated white matter integrity in FEP patients with PNS.
METHODS: WHITE MATTER ALTERATIONS IN PNS

We measured FA values in these regions of interest in FEP patients with PNS (12), without PNS (52) and controls (52).
PRELIMINARY FINDINGS

![Graph showing statistical data](image)

* p < 0.05

<table>
<thead>
<tr>
<th>Background</th>
<th>Defining PNS</th>
<th>Memory and PNS</th>
<th>Neural Correlates of PNS</th>
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</table>
PRELIMINARY FINDINGS

1. Uncinate Fasciculus: Connects orbitofrontal cortex and temporal lobe

2. Uncinate Fasciculus: Critical structure in emotion and memory

3. Lower FA in UF correlated with negative symptom severity and verbal memory impairments (Szesko et al. 2008)

4. Fornix: Connects the hippocampal formation to the prefrontal cortex
CONCLUSIONS

1) Reduced GM in frontal and parahippocampal gyrus in FEP
2) Reduced white matter integrity in FEP specific to fronto-temporo-limbic structures

Poorer verbal memory in FEP

Present before onset of psychosis??

Patients with PNS

Improve with cognitive remediation?

Poorer functional outcome in FEP

Background  Defining PNS  Memory and PNS  Neural Correlates of PNS  Conclusion
ACKNOWLEDGEMENTS

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• Dr. Malla
• Dr. Joober
• All PEPP Staff
• All clients who participated in our studies
Dr. Mallar Chakravarty
Dr. Brodeur and his lab members
FRSQ for providing me with my doctoral funding
EXTRA SLIDES
PEPP LONGITUDINAL STUDY

Assessment of clinical symptoms

0 1 2 3 6 9 12

SOFAS
Neuropsychological Evaluation
MRI/DTI

Background          Defining PNS          Memory and PNS          White Matter and PNS          Conclusion

SOFAS
Neuropsychological Evaluation
MRI/DTI
Deficit Syndrome

- Well-defined
- Prevalence: 15-20%
- Primary negative symptoms
- Present for a min of 12 months
- Identified using the Schedule for Deficit Syndrome (min of 2 out of 6)

Persistent NS

- No clear criteria
- Prevalence: 15-40%
- Primary or secondary negative symptoms
- Present for a min of 6 months
- Identified using any validated negative symptom scale
RESULTS - PREVALENCE

158 FEP

PNS_1
27.8% PNS
n=44
72.2% non-PNS

PNS_2
13.3% PNS
n=21
86.7% non-PNS

PNS_H
13.3% PNS
n=21
86.7% non-PNS
1) PNS_1: score of ≥3 on *at least 1 global item* of the SANS (Malla et al., 2004)
2) PNS_2: score of ≥3 on *at least 2 global items* of the SANS (Edwards et al., 1999)
3) PNS_H (Hybrid): score of ≥3 on either one or both of the subdomains (Foussias and Remington, 2010):

- Diminished Expression
- Amotivation
- Avolition/Apathy
- Anhedonia/Asociability
- Affective Flattening
- Poverty of Speech
RESULTS

- **Baseline Month 12 SOFAS Scores**
  - PNS_1
  - Non-PNS
  - PNS_2

**Background**
- Defining PNS
- Memory and PNS
- Neural Correlates of PNS

**Conclusion**
# FEP Patients in PNS Group

## Frequency

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number of Patients</th>
</tr>
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<tbody>
<tr>
<td>Affective...</td>
<td>5</td>
</tr>
<tr>
<td>Alogia</td>
<td>2</td>
</tr>
<tr>
<td>Avolition-Apathy</td>
<td>15</td>
</tr>
<tr>
<td>Anhedonia-...</td>
<td>20</td>
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## Mean SANS Scores

<table>
<thead>
<tr>
<th>Condition</th>
<th>Mean Scores</th>
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<tbody>
<tr>
<td>Affective Flattening</td>
<td>0.5</td>
</tr>
<tr>
<td>Alogia</td>
<td>0.5</td>
</tr>
<tr>
<td>Avolition-Apathy</td>
<td>3</td>
</tr>
<tr>
<td>Anhedonia-Asociality</td>
<td>3.5</td>
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**Background**

**Defining PNS**

**Memory and PNS**

**Neural Correlates of PNS**

**Conclusion**
## HOW ARE PNS DEFINED?

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<thead>
<tr>
<th>Author</th>
<th>PNS Definition Applied</th>
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<tbody>
<tr>
<td>Galderisi et al. 2012</td>
<td>PANSS score &gt; 3 on a min of 1 NS item</td>
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<tr>
<td>Stauffer et al. 2012</td>
<td>PANSS score &gt; on min of 3 NS items</td>
</tr>
<tr>
<td>Buchanan et al. 1998</td>
<td>Total score of ≥ 20 OR a score of ≥2 on at least 1 SANS global item</td>
</tr>
<tr>
<td>Edwards et al. 1999</td>
<td>SANS HI score of ≥3 on 2 or more of global subscales SANS LOW score of ≥2</td>
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