Cognition-emotion interaction, sex/gender differences and cerebral function in schizophrenia

Adrianna Mendrek, Ph.D.
Dept. Psychology, Bishop's University,
Centre de recherche Institut Universitaire en Santé Mentale de Montréal

Marc Lavoie, Ph.D.
Dept. Psychiatry, Université de Montréal
Centre de recherche Institut Universitaire en Santé Mentale de Montréal
Schizophrenia Overview

- **Schizophrenia is a complex psychiatric disorder:**
  - Positive symptoms (e.g. hallucinations, delusions).
  - Negative symptoms (e.g. blunted affect, social withdrawal).
  - Disorganized symptoms (e.g. speech, thought, and behavior).

(American Psychiatric Association [DSM-5], 2013)

- **Lifetime prevalence: 0.5-1% worldwide** (Drake et al., 1998; Goldner et al., 2008).

- **Typically poor outcome and decreased quality of life** (Alptekin et al., 2004; Browne et al., 2007; Jobe and Harrow, 2005).

- **Rate of suicide: 10-15% (50% attempted)** (Andreason & Carpenter, 1993; Saha et al., 2007).
Sex differences in schizophrenia:

- earlier in males by approximately 1-3 years at 1st peak, however:
  - not universally found
  - no difference in familial schizophrenia
  - no difference in offspring of older fathers

- 2nd peak around menopause found only in women

- more premorbid deficits and more negative symptoms in men than in women

Age at first sign of schizophrenia (N=248) (Hafner et al 1993)
Sex differences in schizophrenia: brain structure

- Men have larger ventricles than women (Andreasen et al 1990)
- Smaller overall frontal and temporal lobe volumes (Andreasen et al 1994; Reite et al 1997; Bryant et al, 1999; Gur et al 2000)

- Altered sexual dimorphism
  - Anterior cingulate (Goldstein et al., 2002; Takahashi et al., 2003)
  - Amygdala and orbitofrontal cortex (Gur et al., 2004; Frazier et al., 2009)
Methods

• Neuroimaging:
  – fMRI (BOLD 3T) &
  – ERPs (56 EEG electrodes)

• Tasks:
  – emotion processing
  – visuo-spatial abilities
  – emotional memory

• Hormones
  – estrogen
  – progesterone
  – testosterone

• Gender role and identity (BSRI)
Participants

- 42 schizophrenia patients (21 women) clinically stable
- 42 controls (21 women)
- Groups matched for age, handedness and parental SES
- Men and women patients equivalent in positive, negative and total symptom severity (PANSS)
- All patients medicated with atypical antipsychotics (e.g., olanzapine, quetiapine, or low doses of risperidone) to reduce potential hyperprolactenemia
Mental rotation task

- on each trial the subject has to decide whether the two shapes are identical, or if one is a mirror image of the other
Mental rotation
behavioral data

(Jimenez et al 2009)
BOLD activations during mental rotation vs. reference task

Control men

Control women

Patient men

Patient women

(Jimenez et al. 2010; Mendrek et al., 2011)
Emotional Memory task

Presentation of positive (high and low arousal), negative (high and low arousal) and neutral images - IAPS collection
Recognition accuracy in healthy and schizophrenia men and women

Recognition accuracy in healthy and schizophrenia men and women
Brain activations during recognition memory of negatively valenced images

Control women minus schizophrenia women

Schizophrenia men minus control men

Women

Men
Brain activations during recognition memory of positively valenced images

Control women minus schizophrenia women

Schizophrenia men minus control men

Women

Men
Emotional memory in schizophrenia: An ERP study

Marc Lavoie
Memory of emotional pictures
(performances)

• Controls
  – Better recognition to high arousal pictures (Neumann et al., 2007; Gasbarri et al., 2006)
  – Delayed reaction times for unpleasant as compared to pleasant pictures (van Strien et al., 2009; Glaser et al., 2012).

• Sz patients
  – More accurate for pleasant than for unpleasant pictures (Danion et al., 2003; Neumann et al., 2006; 2007).
## Memory of emotional pictures

(Electrophysiology)

<table>
<thead>
<tr>
<th>Controls</th>
<th>Sz patients</th>
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<tbody>
<tr>
<td>– Pleasant VALENCE increased earlier frontal (N200) components (Glaser et al., 2012)</td>
<td>– Higher physiological responsivity to pleasant emotional content (Hempel et al., 2005).</td>
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<tr>
<td>– Higher AROUSAL affect later (LPC) more parietal components (Dolcos &amp; Cabeza., 2002; Glaser et al., 2012).</td>
<td>– Reduced LPC (parietal) components in pleasant vs neutral (VALENCE) (Horan et al., 2010).</td>
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<td>– No previous study combining emotional pictures’ episodic memory, ERPs and Sz.</td>
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Aims and hypotheses

• **Aims**
  – Investigate the electrophysiological correlates of episodic emotional memory in Sz patients.
  – Evaluate the separate contribution of emotional valence and arousal in episodic memory in a population of women with Sz.

• **Hypotheses**
  – Based on acknowledged emotion processing deficits in Sz patients, we have predicted a poorer memory performance.
  – In Sz patients, the ERP old-new effect (episodic memory) will be reduced, particularly in response to emotional images.
    • Early (within 300 ms) frontal o-n effect reduction in response to VALENCE
    • Late (after 400 ms) parietal o-n effect reduction in response to AROUSAL
Participants and evaluation

- 17 Control women
- 17 WOMEN with schizophrenia (Sz)

- Handedness: All right handers
- Mean age: 31 yrs old (no significant group differences)
- Intelligence: Normal range (Raven test)
- SES: Comparable in both groups

- All patients were in a stabilized stage of their disease.
- Actual Medications | clinical group: CPZ equiv = 510 mg.
- Schizophrenia diagnosis by trained psychiatrist (DSM-IV-TR).
- Positive & Negative Syndrome Scale
  - PANSS = 41
  - Positive = 18
  - Negative = 19
Event-Related Potentials measures

- ERPs were obtained from 56 EEG electrodes

- Two components were extracted
  - 200-300 ms (frontal N200) - Familiarity
  - 400-900 ms (central-parietal LPC) - Conscious recollection
International Affective Picture System - women norms
[orthogonal design]

High arousal - Low valence (Unpleasant)
High arousal - High valence (Pleasant)
Low arousal - Low valence (Unpleasant)
Low arousal - High valence (Pleasant)

Arousal
High
Low

unpleasant  neutral  pleasant
Episodic memory protocol

- **Study design**
  - 200 images
    - Study phase (100 items)
    - Test phase (100 new + 100 old)
  - 25 images per category
    - LV – LA  Unpleasant
    - LV – HA
    - HV – LA  Pleasant
    - HV - HA

- **Statistics**
  - MANOVA factorial design
    - Memory (2) by valence (2) by arousal (2) by hemisphere (2)

- 40 minutes study-test delay
- 4000 ms
- 2000 ms - variable
- Keyboard press
- old  new
RESULTS
After the EEG recording, all participants assigned a subjective score to each of the images they were exposed to during the ERP session.
Discrimination accuracy

[Valence by arousal by group | F(1,31)=13.33, p<.001]

- **Control**
  - Diminished performance for unpleasant high arousing pictures.

- **Sz**
  - For pleasant pictures, patients have reduced performances compared to the control group (high and low arousal).
  - For unpleasant pictures, patients have better performances than the control group for high arousal pictures.
N200 frontal region (valence effect)

Left hemisphere

Right hemisphere

Pleasant

Unpleasant

Old

New
Frontal N200 amplitude (old new effect)

[Memory by valence by hemisphere by group | F(1,32)= 8.36, p=.007]

Schizophrenic:
- reduced o-n effect in the RIGHT hemisphere for the pleasant stimuli.
- reduced o-n effect in the LEFT hemisphere for the unpleasant stimuli.
LPC central region (arousal effect)

High arousal

Low arousal

Sz
Control

Old
New
Central LPC (old-new effect 400 -900 ms)
Memory by arousal by hemisphere by group [F(1,32)= 5.51; p=.02]

Schizophrenia:
- reversed o-n effect in for the high arousal images.
- absence of o-n effect for the low arousal.

Old minus new amplitude subtraction

- High arousal
- Low arousal

LH+    RH+
LH-    RH-
Conclusion

Emotional valence and early frontal ERPs

– Emotional **valence** mainly impact on episodic memory in **early** temporal windows (familiarity).
  
  • Unpleasant images diminished performances in Sz
  
  • Familiarity: reduced N200 in Sz (100-300 ms)
    
    – Unpleasant images diminished old-new effect (in the left hemisphere).
    
    – Pleasant images diminished old-new effect (in the right hemisphere)
Conclusion
Emotional arousal and late parietal ERPs

– Emotional arousal mainly impact on episodic memory in posterior regions

  • Conscious recollection - LPC (400-900 ms).

  – Diminished or inverted old-new effect in Sz in response to high arousal images.

  – Partly consistent with Horan et al., 2010 (emotional ERPs (LPC) in Sz).
Take home message I...

- These findings provides further support for the notion of a possible discrepancy between the subjective emotional experience and the physiological expression of emotions in patients with schizophrenia.
Take home message II

- Patients with schizophrenia showed altered processing of
  - *Familiarity* (N200) for unpleasant pictures when arousal are maintained equivalent across valence categories.
  - *Conscious recollection* (LPC) for highly arousing pictures regardless of valence.
Future directions

- More sex differences...
  - Hormonal status (Testosterone, oestrogen, progesterone)
- Integration between brain imaging / ERPs
- ... and many other things
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