Department of Neurosciences
School of Medicine
University of Padua

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COGNITIVE FUNCTIONING AND DECISION MAKING IN ANOREXIA NERVOSA: RISK FACTORS AND PROGNOSTIC IMPLICATIONS

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Cognitive assessment in AN: Why?

Original Investigation

AN patient were more left-handed than controls: OR=2.8, 95% C.I. 1.1-7.2

AN controls

Handedness

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Perinatal complications as risk factors for impairment of executive functions in AN

Subjects with lifetime AN (n=193) and controls (170)

Structured clinical interview for ED

Neuropsychological assessment

- set-shifting (WCST, Trial A and B)
- visuo-spatial impairment (Rey Complex Figure)
- decision making (Iowa Gambling Task)
- working memory (interference)

Genetic assessment (ongoing)

COMT, BDNF, 5HT transporter
Wisconsin Card Sorting Task

Perseverance, set-shifting deficit
Cognitive inflexibility

Cognitive functioning

Total errors* perseveration*
Wisconsin Card Sorting Task

Perseverance, set-shifting deficit

Cognitive inflexibility

Cognitive functioning

Press 1-4 to sort card
Rey-Osterrieth Complex Figure Test

AN: Deficit in central coherence

It appraises different cognitive functions such as perception, visuospatial ability, planning and visuospatial memory. The subject must copy and recall, after an interval of three minutes, a complex geometric figure.

The index of central coherence (ICC), that derives from the order of construction index and style index.
Central coherence

Rey-Osterrieth Complex Figure Test

Deficit in central coherence

![Graph showing copy, recall, and central coherence scores for AN and controls.]
Central coherence

Rey-Osterrieth Complex Figure Test

Deficit in central coherence

![Graph showing comparison between AN, controls, and sisters in copy, recall, and central coherence tasks.](image)
Visuo-spatial abilities

Figure aggrovigliate
Ricostruzione oggetti
Block design

AN
controls

overlapping*
object assembly*
block unsegm*
block segm*
Visuo-spatial abilities

Figure aggrovigliate
Ricostruzione oggetti
Block design

AN
controls
sisters
Impairment in executive functioning is not a function of brain atrophy

37 years old
24 years of AN
BMI of 10.4

WCST n. persever. 13% (normal)
TMT B = 98 (normal)
Rey Figure ICC = 1.06 (normal)
Rey copy = 26 (low)
Rey memo = 15 (normal)
IOWA net score = -2 (low)

23 years old
4 years of AN
BMI of 16.1

WCST n. persever. 36% (high)
TMT B = 152 (high)
Rey Figure ICC = 1.06 (normal)
Rey copy = 32 (low)
Rey memo = 12 (low)
IOWA net score = -2 (low)
But weight status can change the relationship between cognitive function and genetic polymorphisms.

**Figure:**

- PFC Functioning
- High dopamine
- Normal dopamine

**Dopamine Concentrations**

BIOL PSYCHIATRY 2007;61:626–632
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Decision making

- Complex process guided by both cognitive and emotional issues.
- Ability to consider future consequences in order to obtain the best gain in the long term.
Brain and decision-making

Dorsolateral Prefrontal cortex = cognitive component: planning, reasoning, learning from errors, and delaying actions

Ventromedial Prefrontal cortex and insula = emotional component: impulsive choice towards immediate gain, but also automatic intuition about good choices for the future (somatic marker hypothesis)
Iowa Gambling Task (IGT)

The IGT has been used as a behavioral indicator of risky decision making that may reflect dysfunction of frontal lobe structures or frontal connections.
Iowa Gambling Task
Iowa Gambling Task

General Performance

Net score = (number of choice of good decks) – (number of choices of bad decks)

Learning score = (number of good choices in the last 40 decks) – (number of good choices in the first 40 decks)

Expectancy-Valence model
(estimation of cognitive parameters)

a = attention to recent outcomes (updating) as opposite of persistence on initial choices (from 0 to 1)
w = attention to wins as opposite to attention to losses (from 0 to 1)
c = choice consistency during the task (from -5 to 5)
Iowa Gambling Task

Yechiam, Busemeyer, Stout, & Bechara, 2005
Our study

A sample of
168 subjects with lifetime AN
169 healthy controls

- Structured diagnostic interview
- Iowa Gambling Task

Other cognitive measures:
- Wisconsin Card Sorting Test
- Rey Complex Figure
- Interference memory test (working memory)
Iowa Gambling Task

IGT net score:  
t=5.17; p<0.001

IGT learning:  
t=3.35; p=0.001
Iowa Gambling Task

No difference
Expectancy-Valence model

\[ a: \ 0.36 \pm 0.40 \text{ among controls}; 0.33 \pm 0.40 \text{ among AN}; t=0.56; p=0.58 \]
\[ w: \ 0.46 \pm 0.31 \text{ among controls}; 0.40 \pm 0.33 \text{ among AN}; t=2.00; p<0.05 \]
\[ c: \ 0.75 \pm 1.67 \text{ among controls}; 0.60 \pm 1.81 \text{ among AN}; t=0.41; p=0.68 \]

Given the high variance in the EV model parameters in both AN and controls, we performed a cluster analysis.

Two clusters emerged:

Cluster 1 (‘perseverative’)
- low a (low updating)
- low w (strong attention to losses)
- high c (high consistency)

Cluster 2 (‘impulsive’)
- high a (high updating)
- high w (strong attention to wins)
In AN, the two clusters did not show significant differences. Among controls, the impulsive cluster reported a poorer performance, due to low learning.
Yechiam, Busemeyer, Stout, & Bechara, 2005
In AN, the two clusters showed significant differences:

The impulsive cluster in comparison to the perseverative is associated to:
- younger age of onset (p<0.02)
- higher number of perinatal hypoxic complications (p<0.05)

- In the impulsive cluster (less true in the perseverative), a good performance is associated to good response to treatment.

In the perseverative cluster, a good performance is associated to:
- low cognitive inflexibility
- absence of met allele in BDNF val66met polymorphism
- presence of met allele COMT val158met polymorphism
Conclusions

Decision making is significantly impaired in AN patients.

However, some patients are unable to make good decisions because of their impulsiveness and inability to delay gratification and learn from errors, while others are so perseverative and avoidant that fail to learn during the task.

This distinction may have important implications for phenotype characterization and treatment, because they are associated to different genetic and environmental risk factors.
Prenatal and perinatal factors: Why are they important?

Two possible pathways:

- Prenatal/perinatal hypoxic complications = damage of specific brain structures resulting in cognitive impairment

- Developmental dysfunction of stress response systems due to fetal programming = inability to cope with stressful situations or trauma, effects on brain development
Perinatal Factors and the Risk of Developing AN

Risk of developing AN

<table>
<thead>
<tr>
<th>Number of Complications</th>
<th>0</th>
<th>1 to 5</th>
<th>&gt; 5</th>
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<tbody>
<tr>
<td>Risk of developing AN</td>
<td>10.5</td>
<td>17.7</td>
<td>28</td>
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</table>

AN onset

<table>
<thead>
<tr>
<th>Number of Complications</th>
<th>0</th>
<th>1 to 5</th>
<th>&gt; 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>AN onset</td>
<td>19</td>
<td>18.5</td>
<td>17</td>
</tr>
</tbody>
</table>

OR = 1.8 3.3

(1.1-3.2) (1.6-6.6) (Kruskal-Wallis $\chi^2=7.73$; d.f.=2; $p<0.03$)
Perinatal complications as risk factors for impairment of executive functions in AN

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Structured clinical interview for ED

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Perinatal history

Obstetric clinical records for 117 AN and 88 control subjects
(86 AN and 61 controls born in Padua Hospital)

Genetic assessment (ongoing)

COMT, BDNF, 5HT transporter
Perinatal complications as risk factors for impairment of executive functions in AN

Interactions with other risk factors (genetic) are probable, because most subjects with perinatal complications did not display psychopathology or cognitive impairment.

Central coherence index is correlated with the number of hypoxic complications in AN (F(1, 81)=7.96; p=0.006).

BDNF (val66met polymorphism)

Absence of met allele: F(1, 36)=0.68; n.s.

Presence of met allele: F(1, 24)=13.21; p<0.001
Two possible pathways:

- Prenatal/perinatal hypoxic complications = damage of specific brain structures resulting in cognitive impairment

- Developmental dysfunction of stress response systems due to fetal programming = inability to cope with stressful situations or trauma, effects on brain development
The interaction between perinatal factors and childhood abuse in the risk of developing anorexia nervosa

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Stress and Brain

The effects of stress are correlated to brain maturation at the time of trauma.

<table>
<thead>
<tr>
<th></th>
<th>Prenatal stress</th>
<th>Postnatal stress</th>
<th>Stress in adolescence</th>
<th>Stress in adulthood</th>
<th>Stress in aging</th>
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<tbody>
<tr>
<td></td>
<td>Birth</td>
<td>2</td>
<td>8</td>
<td>18</td>
<td>30</td>
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<td>Amygdala</td>
<td></td>
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<td>Frontal cortex</td>
<td></td>
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<td></td>
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<tr>
<td>Hippocampus</td>
<td></td>
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</table>

Effect on HPA axis:
- Programming effects
- Differentiation effects
- Potentiation/incubation effects
- Maintenance/manifestation effects
- Maintenance/manifestation effects
Fetal programming hypothesis

Cortisol exposure during pregnancy

Neonatal dysmaturity

Lower glucocorticoid receptor expression in the hippocampus (HPA hyperactivity)

Increased glucocorticoid receptor expression in the amygdala (increased anxiety and avoidance responses)

Fig. 3. Prenatal dexamethasone programmes the brain

Increased glucocorticoid receptor expression in the amygdala (increased anxiety and avoidance responses)

increased re-uptake sites

hippocampus

amygdala

GR

MR

CRH

GR

MR

CRH

5HT

PVN

raphé

pituitary

adrenal

CORT
Assessment of stress during pregnancy

Interview with parents (the mother or both parents) about pregnancy for 113 AN and 84 control subjects.

Subjective distress:
4 questions about feelings and distress during pregnancy

Objective stress
structured interview investigating a list of stressful events (aggressions, death of loved ones, car accidents, natural disasters, conflicts with partner or separation), their severity and time during pregnancy.
Mothers of AN patients reported more often than mothers of controls (64% vs. 48%; $\chi^2=4.55; \text{df}=1; p=0.03$) a stressful event during pregnancy.

In addition, the number and severity of stressful events was greater in mothers of AN patients ($p<0.002$).

Subjective maternal distress during pregnancy was higher in mothers of AN than in mothers of controls, but the difference was not significant. $1.6 \pm 2.1$ vs. $0.9 \pm 1.0$; $z = 1.60; p=0.10$
In both AN patients and controls, maternal stress during pregnancy was associated to lower Edinburgh scores (p=0.02 in AN, p=0.07 in controls).

In AN, maternal stress was associated with:

- Higher number of perinatal complications (p<0.001)
- Higher number of pregnancy complications (p<0.006)
- Higher number of neonatal dysmaturity signs (p<0.05)
- Higher perfectionism (p=0.03)
- Higher persistence at TPQ (p=0.004)
- Higher WCST perseverative errors (p=0.002)
- Poor global score WCST (p=0.01)
Conclusions

Cognitive functioning is impaired in anorexia nervosa and both genetic and early environmental risk factors are implicated.

Prefrontal dopamine and COMT polymorphism have important effects on cognitive perseveration in anorexia nervosa.

Hypoxic perinatal complications might be risk factors for lower central coherence in AN, and BDNF probably impact recovery from neonatal hypoxia.
Stressful events are more often reported by mothers of AN patients than by mothers of healthy controls, but they did not report significantly more subjective distress during pregnancy.

Maternal reporting of stress during pregnancy seems to be associated to ‘core’ AN symptoms, such as perfectionism and temperamental persistence, but also to cognitive inflexibility and lower levels of right-handedness.
Many thanks to all the Padova group!

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and

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