Cognitive Impairment in Bipolar Disorder: What is new in the field?

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Bipolar Disorder

Benign prognosis?

- Sub-syndromal symptoms (Judd et al. 2002)
- Functional recovery may only happen in a third
- Cognitive impairment may persist in remission and probably determine outcomes
Aims of Talk

• Cognitive impairment in mania, depression and euthymia
• Associations between cognitive impairment and functioning in BD
• Update this audience on cognitive studies in BD in later life.
Mania: DSM V refers to cognitive features

**Distractibility** i.e. attention drawn too easily to unimportant or irrelevant external stimuli as reported or observed

(Excessive involvement in activities have a high potential for painful consequences)
Bipolar Depression
DSM V

“Diminished ability to think or concentrate, or indecisiveness, nearly every day”
Mania and Depression

• Generalised cognitive impairment in bipolar depression: Attention, memory, executive function, psychomotor function and reaction times (Savard 1980, Wolfe et al. 1987; Martinez-Aran et al. 2004; Rubinsztein 2006, Mahli et al. 2007)

Differences between mania and depression?

• No or marginal differences in cognition were shown between depressed and manic / hypomanic states (Bulbena and Berrios 1993; Goldberg et al. 1993; Martinez-Aran et al. 2004; Volkert et al. 2016).

• However, these studies employed “neutral” tasks not relevant to the patient’s mood.

• We demonstrated differences in mania vs unipolar depression in task engaging “emotional processing” (Murphy et al. 1999; Murphy et al. 2001; Rubinsztein et al. 2008).
Murphy et al. 1999

Depressed patients exhibited an affective bias for negative stimuli, manic patients showed the opposite.
Murphy et al. 1999: Manic patients
Bipolar depression vs Controls
(Rubinsztein et al. 2006)

<table>
<thead>
<tr>
<th>Neutral (non-emotional) cognitive tasks</th>
<th>Controls</th>
<th>BP Depressed</th>
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<tbody>
<tr>
<td><strong>SMTS</strong></td>
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<tr>
<td>Proportion correct (PC)</td>
<td>0.97 (0.01)</td>
<td>0.97 (0.01)</td>
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<tr>
<td>latencies</td>
<td>2920 (168)</td>
<td>3730 (235)*</td>
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<td><strong>DMTS</strong></td>
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<td>PC (across all delays)</td>
<td>0.83 (0.02)</td>
<td>0.73*</td>
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<tr>
<td>latencies</td>
<td>3324 (168)</td>
<td>3952 (260)</td>
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<tr>
<td><strong>Pattern recognition memory</strong></td>
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<tr>
<td>PC</td>
<td>0.87 (1.7)</td>
<td>0.8 (2.6)</td>
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<tr>
<td>latencies</td>
<td>2118.5 (0.48)</td>
<td>2617 (278)</td>
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<tr>
<td><strong>Spatial recognition memory</strong></td>
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<tr>
<td>PC</td>
<td>0.79 (2.4)</td>
<td>0.70 (2.4)</td>
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<tr>
<td>latencies</td>
<td>2428 (153)</td>
<td>2615 (189)</td>
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<tr>
<td><strong>Attentional set shifting</strong></td>
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<td>Stages completed</td>
<td>8.8 (0.1)</td>
<td>8.04 (0.2)</td>
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<td>errors at ED shift stage</td>
<td>12.3 (1.6)</td>
<td>16.5 (2.4)</td>
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<td><strong>NTOL</strong></td>
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<tr>
<td>PC (across all delays)</td>
<td>0.64 (0.05)</td>
<td>0.58 (0.03)</td>
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</table>
Cognitive changes in Euthymia

Explosion of studies in euthymia: 1990-2000s

Studies need to show that patients are truly euthymic and/or to control for affective symptoms.

Metanalysis of effect sizes (Robinson et al. 2006)

Fig. 1. Results of the meta-analyses (effect sizes plus 95% confidence limits). DSST, Digit Symbol Substitution Test; CPT, Continuous Performance Test; WCST, Wisconsin Card Sorting Test.
Do all BD patients in euthymia have CI? What is prevalence? (Cullen et al. 2016)

At 5th percentile impairment threshold, prevalence ranges in community dwelling adults aged 18-70, recruited consecutively

- Executive Function 5.4-58%
- Attention/Working Memory 9.6-52%
- Speed/reaction time 23-44%
- Verbal memory 8.2-42%
- Visual memory 12--33%
Ecologically valid tests of CI in BD  
(O’ Shea et al. 2010)

• No definitive relationship between performance on neuropsychological test batteries and the ability to cope in life

• Ecologically valid tests may bridge this gap
• BPD- Euthymic pts showed CI on Ecologically valid tests of
• attention -Test of Everyday attention (TEA),
• memory -Rivermead Behavioural Memory Test (RBMT)
• executive Function -Behavioural Assessment of the Dysexecutive Syndrome (BADS)
• Poor attention α Unemployment (O’ Shea 2010)
RBMT-E (O’Shea et al. 2010). $p = <0.001$, $ES = 0.52$, (6/12 tests significant)
O Shea et al. 2010 TEA p<0.001 (ES -0.52)
(5/10 significantly impaired)
Question:

• Does cognitive impairment correlate with functioning in BD?
Does CI correlate with functioning
(Baune and Mahli, 2015)

• Relationships between cognitive function and general function in patients with BD
• in both symptomatic and euthymic patients with BD.

• Cognitive function may be a better predictor of long term general function than clinical severity measures.
Does CI correlate with functioning

(Baune and Mahli, 2015)

• General measures of functioning (e.g. GAF) show more inconsistent associations with cognitive function.

• Domain specific scales of social and occupational function (WHO-DAS, FAST, MSIF or assessing occupational status may be better suited to obtain realistic associations between cognition and general and domain specific function.
Other factors influencing cognitive impairment

• More severe longstanding illness $\alpha$ CI (review by Cullen et al. 2016)

• Episodes of mania, depression (less so), no of hospitalisations, length of episodes correlates with CI (Robinson and Ferrier 2006)

• Antipsychotic medication (but not lithium/AD/anticonvulsants) $\alpha$ CI (Cullen et al. 2016)*

*Patients with Alcohol and Substance misuse are rarely included in studies and correlations (Cardoso et al. 2016- showed no difference)

* Smoking and cardiovascular risk factors may also be relevant but simply not studies in association studies
Ongoing issues in literature

• Most studies of cognition are cross sectional
• What happens longitudinally?
Longitudinal Evaluations (not consistent for domain across studies but not declining!)

- 2 yr f/u in euthymic BD treated with lithium (Mur et al. 2008): Impairment in executive function and processing speeds remained (similar findings Braw et al. 2013)

- 55 BP (manic and depressed tested): global deficits.
- 29 f/u: Cognitive impairments partially recovered after at least 3 months of remission.
- Working memory and Verbal memory remained poor. (Volkert et al. 2016)
Longitudinal Studies:

5 year f/u of executive functioning (EF) (Ryan et al. 2016):
• Older age at baseline was associated with worse initial performance in EF.
• EF impairment persisted over time
• Age and having a BD diagnosis together, do not accelerate EF decline

5 year f/u: (Santos et al. 2014)
• Speed of processing, WM, attention, VM, Visual M, EF
• Persistent and stable after 5 years, Verbal recall a bit worse.
Question: Are drugs contributing to CI in BD?
Do drugs contribute to CI in BD

Cognitive deficits are still evident in euthymic medication–free patients (Goswami et al. 2002)

Lithium:
• No significant effects (Lopez-Jaramillo 2010; Muralidharan et al. 2015) and on a longitudinal 6 year f/u - effects were stable (Engelsmann et al. 1988)
• Biggest effect on psychomotor performance (ES 0.62) (Wingo et al. 2009)
• Psychomotor performance and verbal memory (subtle but definite effects) (Dias et al. 2012)

Effects of Antipsychotics, anti-epileptics and benzodiazepines has not been well evaluated.

Lamotrigine better than CBZ, Valproate for cognition
Are there effective treatments for CI in BD?
Treatments for CI in BD:

Drug treatments: promising but need replication

• Erythropoietin (neurotrophic actions) (Miskowiak et al. 2014)
• Mifepristone (antiglucocorticoid) (Young et al. 2004) Aspects improved (Spatial WM/VF, Spatial Recognition memory)
• Pramipexole (dopamine agonist) improved processing speed and working memory in DBPCT in euthymic subgroup (Burdick et al. 2012)
• N- Acetyl cysteine (an anti-inflammatory and antioxidant) did not work (Dean et al. 2010)
Psychological treatments: promising

- Cognitive Remediation for depression (Lee et al. 2013; Naismith et al. 2010)
- Functional remediation (Torrent et al. 2013)
Neurocognitive changes in euthymic patients and their unaffected relatives: (Cardenas et al. 2016; Balanza-Martinez et al. 2008)

- Patients, and less so, relatives show impairments in attention, processing speeds, verbal learning/memory and verbal fluency.
- Studies were more likely to find impairments in patients than relatives, suggesting some cognitive impairment is due to the illness itself and/or its treatment.
- But issues with studies:
  - smaller sample sizes in relatives, differences amongst relatives studies, assessment instruments may contribute towards inconsistencies in neurocognitive performances
Question?

• Is CI neurodevelopmental or neuroprogressive
Cognition in early stages of BPD

• First episode Manic pts who then become euthymic show widespread CI which does not resolve (Daglas et al. 2016)

• Cross Sectional studies of first episode pts show generalised CI (Metanlyses by Frias et al. 2014; Lee RS et al. 2014, Bourne 2013).

• Prospective study in unaffected high risk subjects.

• Those that developed depression within 2 years showed decreased ED set shifting abilities. (Papmeyer et al. 2016)
Unlike Schizophrenia....(not likely to be a neurodevelopmental disorder)

• Less than in SZ (Mesholam- Gately et al. 2009)

• BD may be seen as a neuroprogressive disorder with a subtle neurodevelopmental component immediately prior to illness onset (Lewandowski et al. 2011)
Questions in Later life:

• Is CI in later life euthymic patients similar/ worse than that seen in younger patients?

• Is CI worse in patients with LO- BD vs EO- BD?
Cognitive changes in later life BD in Euthymia


- Cognitive changes seen in older patients relative to age matched controls similar to those seen in younger pts:
  - Information-processing speed
  - **Executive function** (not Delaloye et al. 2009)
  - **Verbal memory** (Pennarts et al. 2014 n=53; Schouws et al. 2009, but not others Gildengers et al. 2007, n=20)
Cognitive changes in later life BD in Euthymia
(Samame et al. 2013)

• Differences are not evident between patients and controls using screening tests like MMSE/ clock drawing tests
• On average cognitive performance of elderly BD between 0.6-0.9 SD below that of healthy subjects
CI in later life BD \cite{Schouws2009} n=109; 78 EO and 60 LO compared with 78 age matched controls

<table>
<thead>
<tr>
<th>Measure</th>
<th>Mean (SD)</th>
<th>Comparison Group (N = 78)</th>
<th>Early Onset Group (N = 59)</th>
<th>Late Onset Group (N = 60)</th>
<th>Patients Versus Comparison Group</th>
<th>Early Versus Late Group</th>
<th>Between Group Contrast</th>
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<tbody>
<tr>
<td>Psychomotor performance</td>
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<tr>
<td>Trailmaking Test Part A, seconds</td>
<td>46.97 (19.6)</td>
<td>63.03 (34.3)</td>
<td>89.78 (68.3)</td>
<td>13.55 &lt;0.01 &lt;0.30</td>
<td>7.2 0.01 0.06</td>
<td>CG&gt;EO&gt;LO</td>
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<td>Mental effort</td>
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<td>ASTM 1 t/m 10</td>
<td>29.00 (1.0)</td>
<td>28.03 (1.6)</td>
<td>26.77 (5.6)</td>
<td>4.41 &lt;0.01 0.12</td>
<td>2.79 0.09 0.02</td>
<td>CG&gt;EO, LO</td>
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<tr>
<td>Attention and executive function</td>
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<td>Digits forward</td>
<td>5.73 (0.9)</td>
<td>5.52 (0.9)</td>
<td>5.08 (0.9)</td>
<td>7.74 &lt;0.01 0.19</td>
<td>1.74 0.19 0.01</td>
<td>CG&gt;EO, LO</td>
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<tr>
<td>Digits backward</td>
<td>4.71 (1.1)</td>
<td>3.93 (0.9)</td>
<td>3.08 (1.0)</td>
<td>11.27 &lt;0.01 0.26</td>
<td>0.07 0.79 &lt;0.01</td>
<td>CG&gt;EO, LO</td>
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<tr>
<td>Trailmaking Test Part B, seconds</td>
<td>109.68 (58.7)</td>
<td>175.41 (118.6)</td>
<td>218.10 (129.4)</td>
<td>14.87 &lt;0.01 0.32</td>
<td>3.54 0.06 &lt;0.01</td>
<td>CG&gt;EO, LO</td>
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<tr>
<td>Stroop Color Word test,* seconds</td>
<td>45.31 (12.8)</td>
<td>61.51 (29.4)</td>
<td>71.40 (33.5)</td>
<td>13.21 &lt;0.01 0.29</td>
<td>2.91 0.09 0.02</td>
<td>CG&gt;EO, LO</td>
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<td>D-A-T</td>
<td>55.75 (10.7)</td>
<td>25.66 (11.0)</td>
<td>21.93 (11.5)</td>
<td>23.06 &lt;0.01 0.42</td>
<td>3.22 0.07 0.02</td>
<td>CG&gt;EO, LO</td>
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<tr>
<td>Animal naming</td>
<td>23.23 (6.0)</td>
<td>18.76 (5.1)</td>
<td>17.83 (5.6)</td>
<td>15.14 &lt;0.01 0.34</td>
<td>0.87 0.35 &lt;0.01</td>
<td>CG&gt;EO, LO</td>
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<td>Occupation naming</td>
<td>17.41 (4.9)</td>
<td>15.39 (5.4)</td>
<td>12.35 (4.8)</td>
<td>11.43 &lt;0.01 0.26</td>
<td>10.32 &lt;0.00 0.08</td>
<td>CG&gt;EO=LO</td>
<td></td>
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<tr>
<td>Mazes, seconds</td>
<td>121.41 (95.32)</td>
<td>156.64 (108.8)</td>
<td>211.38 (140.4)</td>
<td>14.26 &lt;0.01 0.51</td>
<td>5.63 0.02 0.05</td>
<td>CG&gt;EO, LO</td>
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<td>Rule Shift Cards BADS</td>
<td>1.06 (1.0)</td>
<td>1.53 (2.2)</td>
<td>2.70 (2.8)</td>
<td>9.37 &lt;0.01 0.22</td>
<td>6.42 0.01 0.05</td>
<td>CG&gt;EO=LO</td>
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<td>Declarative memory</td>
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<td>10 Words Test</td>
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<tr>
<td>Learning (Trials 1-5)</td>
<td>37.35 (5.7)</td>
<td>30.23 (6.5)</td>
<td>27.73 (7.3)</td>
<td>25.91 &lt;0.01 0.45</td>
<td>3.84 0.05 0.03</td>
<td>CG&gt;EO, LO</td>
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<tr>
<td>Retention</td>
<td>6.74 (1.9)</td>
<td>4.58 (1.9)</td>
<td>4.45 (2.3)</td>
<td>16.99 &lt;0.01 0.34</td>
<td>0.47 0.75 &lt;0.01</td>
<td>CG&gt;EO, LO</td>
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<tr>
<td>Recognition</td>
<td>19.26 (0.9)</td>
<td>18.61 (1.5)</td>
<td>18.09 (2.6)</td>
<td>18.09 (2.6)</td>
<td>18.09 (2.6)</td>
<td>CG&gt;EO, LO</td>
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<td>Visuoconstruction</td>
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<td>Copying AD(S)</td>
<td>12.37 (1.6)</td>
<td>12.27 (1.9)</td>
<td>12.33 (0.8)</td>
<td>12.37 (1.6)</td>
<td>12.37 (1.6)</td>
<td>CG&gt;EO, LO</td>
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<td>Clock drawing</td>
<td>1.41 (0.8)</td>
<td>1.42 (0.8)</td>
<td>1.67 (1.1)</td>
<td>1.41 (0.8)</td>
<td>1.41 (0.8)</td>
<td>CG&gt;EO, LO</td>
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</table>

Notes: ASTM: Amsterdam Short-Term Memory Test; BADS: Behavioral Assessment of the Dysexecutive Syndrome; AD(S): Amsterdam Dementia Screening test; EO: early onset; LO: late onset; CG: comparison group.

*This is a short form consisting of reading the first 4 lines.

*Kruskal-Wallis test patients versus comparison group: for 10 Words Test recognition errors: \( \chi^2 = 34.14, p < 0.01 \); for Figure-copying: \( \chi^2 = 14.79, p = 0.13 \); for Clock drawing, \( \chi^2 = 7.76, p = 0.06 \); Mann-Whitney U test early versus late: for 10 Word Test recognition errors, \( Z = 0.87, p = 0.38 \); for Figure copying, \( Z = -1.08, p = 0.28 \); for Clock drawing, \( Z = -1.17, p = 0.24 \).
Do Cognitive Impairment and functioning correlate:
in later life?

- Info processing speed and Exe fun are related to self care (Pennarts et al. 2014)
- Inf processing and executive function correlate with ADLS – assessed by OT at home (Gildengers et al. 2007)
Does BD- euthymia look like MCI?
(Osher et al. 2011; Silva et al. 2009)

Silva et al. 2009
• Patients with MCI were more impaired in verbal memory, whereas BD patients showed more deficits in attention, motor initiative, calculation and verbal abstraction.
• Half BD subgroup showed deficits in episodic memory similar to MCI patients.

Osher et al. 2011
• BD and MCI pts showed equivalent performance on tests of memory, executive functioning, verbal function and information processing speed
Does CI accelerate with aging in BD? (cross sectional analysis)

- Lewandowski, 2014 used a wide range of ages (18-87)
- Older age was associated with poorer processing speeds in BD (Trail A) but not in comparison subjects. However, not for other cognitive measures. (did not examine VM)
- Suggests that there is accelerated cognitive decline in one domain only
Does CI accelerate with aging? (longitudinal analysis)

• Studies: Contradictory

• With psychotic symptoms over 6 years: accelerated decline observed in one study (Kohler et al. 2013)
• 3 year study: accelerated decline (Gildengers, 2009)

Others show no accelerated decline:
• Mora et al. 2013 (6 years)
• Gildengers et al. 2013 (2 years)
• Burdick et al. 2006 (5 year f/u - improvement in VM and EF)
Conclusions

• Cognitive impairment is widespread in mania and bipolar depression,

• In cross sectional studies of euthymic BD: there are well established impairments in psychomotor performance, attention and executive function, learning and memory

• Some correlations between cognitive impairment and functioning at all ages

• Drugs may be contributing to some of these cognitive changes but unlikely to be whole story