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# Cognition in Major Depressive Disorder

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# Preface

During the past decade, major depressive disorder (MDD) has gone through a significant transformation in its conceptualization from a population health perspective. Rather than the anachronistic and inaccurate description of MDD as a relatively rare, mild, and transient condition, MDD occupies the ignominious position as the leading cause of disability amongst all psychiatric disorders in both developed and developing nations.

The human capital costs attributable to MDD are substantial and increasing. The global economic landscape has gone through a tectonic plate shift wherein the human knowledge economy is the principal determinant of economic competitiveness. Towards the aim of realizing the human potential of individuals (and populations) in this human knowledge economy, optimal psychological and physical health is *sine qua non*.

Emanating and surrounding extant evidence is the observation that cognitive deficits are a core disturbance in MDD, risk factor for illness onset, recurrence, chronicity, and importantly, a principal cause of functional impairment. The latter observation provides the rationale for prioritizing cognitive deficits in the diagnosis, assessment, ongoing evaluation, and treatment of individuals with MDD. Moreover, the identification of cognitive deficits in individuals with MDD provides the impetus for parsing out neurobiological substrates subserving this critical domain of psychopathology.



The overarching aim of this Oxford Psychiatry Library pocketbook is to encourage a pivot towards cognitive dysfunction in MDD. Our hope is to encourage practitioners to probe and evaluate cognitive dysfunction in the clinical ecosystem, and to introduce vistas for future research. Towards the aim of full recovery of MDD (and in the future, prevention of MDD), as well as optimization of individual and population human capital potential, the identification, characterization, evaluation, treatment, and prevention of cognitive dysfunction are warranted.

Roger S. McIntyre

# Symbols and Abbreviations

| | |
|---|---|
| AD | Alzheimer's disease |
| AMPA | α-Amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid |
| ANCOVA | analysis of covariance |
| APTD | acute phenylalanine and tyrosine depletion |
| BC-CCI | British Columbia Cognitive Complaints Inventory |
| BD | bipolar disorder |
| BDI | Beck depression inventory |
| BDNF | brain-derived neurotrophic factor |
| BLC | big/little circle |
| CalCAP | California computerised assessment package |
| CANTAB | Cambridge neuropsychological test automated battery |
| CGI-I | clinical global impression-improvement |
| CGI-S | clinical global impression-severity |
| CGT | Cambridge gambling task |
| CNS | central nervous system |
| COWAT | controlled oral word association test |
| CPFQ | Massachusetts General Hospital cognitive and physical functioning questionnaire |
| CPT | continuous performance task |
| CRT | choice reaction time |
| CSF | cerebral spinal fluid |
| CST | concept shifting task |
| CVLT | California verbal learning test |
| D-KEFS | Delis–Kaplan executive function system |
| DA | dopamine |
| DBS | deep brain stimulation |
| DMN | default mode network |
| DMS | delayed matching to sample |
| DRST | delayed recognition span test |
| DSM-5 | *Diagnostic and Statistical Manual of Mental Disorders (5th edition)* |

| | |
|---|---|
| DSST | digit symbol substitution test |
| DTMS | deep transcranial magnetic stimulation |
| ECT | electroconvulsive therapy |
| FAS | full analysis set |
| fMRI | functional magnetic resonance imaging |
| GABA | gamma-aminobutyric acid |
| GLP-1 | glucagon-like peptide-1 |
| GNAT | go/no-go association task |
| GR | glucocorticoid receptor |
| HAM-A | Hamilton rating scale for anxiety |
| HPA | hypothalamic-pituitary-adrenal |
| HVLT-R | Hopkins verbal learning test revised |
| HRSD | Hamilton rating scale for depression |
| HRSD-21 | Hamilton rating scale for depression (21 items) |
| HRSD-24 | Hamilton rating scale for depression (24 items) |
| IED | intra-extra dimensional set shift |
| IL | interleukin |
| IFN | interferon |
| IST | information sampling task |
| JOLO | judgement of line orientation |
| LOCF | last observation carried forward |
| LNS | letter-number sequencing |
| LTP | long-term potentiation |
| LVLT | Luria's verbal learning test |
| MADRS | Montgomery-Åsberg depression rating scale |
| MCI | mild cognitive impairment |
| MDD | major depressive disorder |
| MDE | major depressive episode |
| MFFT-20 | matching familiar figures test 20 |
| mGlu | metabotropic glutamate |
| MMRM | mixed model for repeated measures |
| MMSE | mini-mental state exam |
| MOCA | Montreal cognitive assessment |
| MR | mineralocorticoid receptor |

| | |
|---|---|
| MST | magnetic seizure therapy |
| NA | noradrenaline |
| nAChR | nicotinic acetylcholine receptors |
| NART | national adult reading test |
| NEAR | neuropsychological educational approach remediation |
| NMDA | *N*-methyl-*D*-aspartate |
| NREM | non-rapid eye movement |
| PAL | paired associates learning |
| PASAT | paced auditory serial addition test |
| PCP | phencyclidine |
| PDQ-D | perceived deficits questionnaire |
| PRM | pattern recognition memory |
| RAVLT | rey auditory verbal learning test |
| RBANS | repeatable battery for the assessment of neuropsychological status |
| RBMT | Rivermead behavioural memory test |
| REM | rapid eye movement |
| RFFT | Ruff figural fluency test |
| RFT | Kimura's recurring figures test |
| ROCF | Rey-Osterrieth complex figure test |
| RTI | reaction time |
| rTMS | repetitive transcranial magnetic stimulation |
| SAMe | S-adenosylmethionine |
| SCWT | Stroop colour-word interference test |
| SD | standard deviation |
| SE | standard error |
| SNRI | serotonin-norepinephrine reuptake inhibitor |
| SOC | stockings of cambridge |
| SRM | spatial recognition memory |
| SRT | Buschke selective reminding test |
| SRT | simple reaction time |
| SSP | spatial span |
| SSRI | selective serotonin reuptake inhibitor |
| SSST | serial sevens subtraction test |

| | |
|---|---|
| SWM | spatial working memory |
| SWS | slow-wave sleep |
| TCAs | tricyclic antidepressants |
| tDCS | transcranial direct current stimulation |
| TMT A | trail making test part A |
| TMT B | trail making test part B |
| TNF | tumour necrosis factor |
| TOL | tower of London |
| TONI-3 | test of nonverbal intelligence-3 |
| TRP | tryptophan |
| UHR-MDD | unaffected healthy relatives of MDD patients |
| VFD | Benton visual form discrimination test |
| VNS | vagus nerve stimulation |
| VPA | verbal paired associates |
| VRM | verbal recognition memory test |
| VRT | Benton visual retention test |
| VSVT | Victoria symptom validity test |
| VVLT | visual verbal learning test |
| WAIS-R | Wechsler adult intelligence test-revised |
| WCST | Wisconsin card sorting test |
| WMS-R | Wechsler memory scale revised |
| WTAR | Wechsler test of adult reading |

## Chapter 1

# Introduction: the relevance of cognitive dysfunction in major depressive disorder

**Key Points**

- Cognitive dysfunction is a core psychopathological dimension of MDD.
- Cognitive dysfunction is documented in both acute and maintenance phases of MDD.
- Cognitive deficits are a principal mediator of psychosocial impairment in many individuals with MDD.



Major depressive disorder (MDD) is a multidimensional mental disorder that affects approximately one in seven individuals at some time in their life (Kessler et al 2012). Major depressive disorder is associated with a high rate of non-recovery and recurrence, with chronicity rates estimated at approximately 20% (van Randenborgh et al 2012). The estimated annual costs attributable to MDD in the USA are approximately $83 billion, with indirect costs due to decreased psychosocial function (notably workforce performance) being a major contributor (Greenberg et al 2003). For example, it is estimated that MDD is associated with an annual loss of 27.2 workdays per ill worker (Kessler et al 2006). The human capital cost attributable to MDD, and the significant reduction in the quality of life, provides the impetus for identifying determinants of functional impairment. Available evidence indicates that cognitive dysfunction is a critical mediator of adverse psychosocial outcomes in this population (Jaeger et al 2006; Conradi et al 2010; Buist-Bouwman et al 2008). For example, the impact of a major depressive episode (MDE) on role functioning and psychosocial outcomes in MDD has been reported to be mediated by impairments in cognition in a substantial proportion of individuals (Buist-Bouwman et al 2008).

The *Diagnostic and Statistical Manual of Mental Disorders* (2013; DSM-5) identifies cognitive impairment (e.g. indecisiveness or lack of concentration) as a criterion for a MDE. Cognitive complaints are commonly reported by individuals with MDD during the symptomatic and 'remitted' phases (Greenberg et al 2003; Kessler et al 2006; Conradi et al 2010; Reppermund 2007). When compared to other mental disorders (e.g. schizophrenia, bipolar disorder (BD)), relatively fewer studies have critically reviewed the affected cognitive domains and estimated the effect sizes of these deficits in younger adults with MDD. In addition, there have been fewer original reports that primarily aim to parse out the neurobiological substrate(s) of cognitive dysfunction, determine the contribution of cognitive dysfunction to psychosocial impairment, and evaluate the procognitive effects of treatment (regardless of modality) in the MDD population.

The mediational contribution of cognitive dysfunction to psychosocial impairment in MDD has become a recent topic of inquiry. Available evidence suggests that cognitive dysfunction is a critical determinant of functional outcomes in MDD (Buist-Bouwman et al 2008). It remains to be determined if the neurobiological substrates that subserve cognitive dysfunction in MDD are discrete, and/or if they overlap with substrates implicated in other mental disorders. Questions regarding which, if any, treatment modality is most effective in mitigating cognitive deficits, preventing their occurrence and/or enhancing cognitive function in MDD, remain unanswered. A general impression, albeit based on relatively few empirical studies, is that cognitive deficits are suboptimally treated with conventional treatment approaches [e.g. selective serotonin reuptake inhibitors (SSRIs)]; (Herrara-Guzman et al 2010; Raskin et al 2007; Millan et al 2012).

The persistence of cognitive dysfunction beyond resolution of the acute episode indicates that in some individuals with MDD it may represent a trait and/or residual phenomenon in some individuals with MDD. Taken together, these results provide the impetus to mentally reconceptualize the definition of 'remission'. Moreover, the moderational influence of cognitive dysfunction on treatment efficacy as well as the influence of cognitive dysfunction on relapse/recurrence vulnerability of MDD has been relatively less studied (Conradi et al 2010). Studies assessing temporality of onset provide evidence that, in a subgroup of younger individuals, cognitive dysfunction may predate the onset of the first MDE (Airaksinen et al 2007). Cognitive dysfunction as an antecedent to MDD is more frequently reported in late onset depression. The preponderance of evidence indicates that cognitive deficits are a consequence as well as a residual phenomenon of MDD, and an antecedent in a smaller proportion of cases.

Cognitive dysfunction in MDD can be disaggregated into two overarching components: 1) General cognitive deficits in one or more non-emotionally valenced domains (e.g. learning and memory, attention, psychomotor speed, executive dysfunction) and 2) processing bias, representing attentional allocation towards negatively valenced stimuli and/or aberrant interpretation of social cues. It has been further hypothesized that cognitive bias represents a trait characteristic in individuals who are temperamentally predisposed to MDD (e.g. neuroticism) (Kendler and Myers 2010).

The effect of conventional antidepressants on cognitive performance has been studied more frequently in non-geriatric individual with MDD; nevertheless, available studies in non-geriatric samples demonstrate that SSRIs, serotonin norepinephrine inhibitors (SNRIs), dopamine (DA) modulators (e.g. bupropion), and norepinephrine inhibitors (e.g. reboxetine) improve cognitive performance in adults with MDD (Furtado et al 2012; Wagner et al 2012; McLennan and Mathias 2010; Herrera-Guzman et al 2010; Herrera-Guzman et al 2008; Ferguson et al 2003). There is also a paucity of evidence comparing the different classes of antidepressants on cognitive function (Herrera-Guzman et al 2010; Herrera-Guzman et al 2008; Ferguson et al 2003). Questions pertaining to the degree that improvement in cognitive deficits can be dissociated from the effect of antidepressants on other domains of MDD psychopathology (e.g. chronicity, subtype, number and duration of MDEs) and/or its co-morbidities have been insufficiently addressed.

This Oxford Psychiatry Library pocketbook aims to emphasize the relevance of cognitive deficits in MDD. Towards this aim we: 1) succinctly review cognitive deficits and

their determinants in adults with MDD; 2) identify the underlying substrates that subserve cognitive deficits; and 3) discuss the effects of different treatment modalities on cognitive performance, proposing treatment approaches that primarily aim to mitigate, reverse, and prevent deficits in cognitive function.

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## Chapter 2

# Measurement and evaluation of cognitive function

**Key Points**

- No measures have been specifically developed to evaluate cognitive function in MDD.
- Existing screening tools for dementia are insufficiently sensitive for evaluating cognitive dysfunction in younger individuals with MDD.
- Notwithstanding the limitations, several existing general and specific measures of cognitive dysfunction can be applied to the MDD population.



The heterogeneity of cognitive batteries and measures, as well as the inclusion of mixed sample compositions and treatment regimens, have contributed to variable findings as it relates to the 'cognitive profile' of MDD. Furthermore, available tests and batteries that measure multiple cognitive domains (e.g., attention, executive function, verbal learning and memory), have not been specifically developed or validated for the detection of cognitive deficits in the MDD population (Table 2.1; McIntyre et al 2013). A separate and replicated observation in adults with MDD is the lack of correlation between subjective and objective measures of cognitive dysfunction (Naismith et al 2007).

Other methodological factors that may affect the interpretation of the available data include, but are not limited to, the comparison of group means without stratification for cognitive dysfunction (e.g. self-reported or observable deficits). For example, an operational definition of cognitive dysfunction could include clinically significant deviation (e.g. 1–2 standard deviations below the age-matched population mean) in one or more cognitive domains (Gualtieri and Morgan 2008). Non-stratified evaluation may inadvertently decrease 'assay sensitivity' and underestimate the magnitude of cognitive deficits in subgroups of individuals with MDD. However, a limitation to deficit stratification based on objective measures is that it potentially precludes individuals with clinically significant deficits (i.e. self-reported cognitive decline but normal objective cognitive performance) from receiving pro-cognitive interventions. The discrepancy between subjective and objective cognitive dysfunction may potentially be due to cognitive reserve (e.g. intelligence, education, occupation; McIntyre et al 2013). Identification of predisposing and resiliency factors for cognitive decline is a research

Table 2.1 Common neurocognitive tests

| Cognitive domain | Neurocognitive tests |
|---|---|
| **Executive function** (concept formation, abstraction, set shifting, set maintenance, planning, self-monitoring, & divided attention) | • Wisconsin Card Sorting Test (WCST)<br>• Trail Making Test Part B (TMT B)<br>• Stroop Colour-Word Interference Test (SCWT)<br>• Categories Test<br>• Block Design (Wechsler Adult Intelligence Test-Revised (WAIS-R))<br>• Picture Completion (WAIS-R)<br>• Concept Shifting Task (CST)<br>• Tower of London (TOL; Cambridge Neuropsychological Test Automated Battery (CANTAB))<br>• Stockings of Cambridge (SOC; CANTAB)<br>• Intra-/extra Dimensional Set Shift (IED; CANTAB)<br>• Spatial Span (SSP; CANTAB)<br>• Ruff Figural Fluency Test (RFFT)<br>• Verbal, Letter, and Category Fluencies<br>• Controlled Oral Word Association Test (COWAT)<br>• The Delis–Kaplan Executive Function System (D-KEFS) |
| **Attention and processing speed** | • Digit Symbol Substitution Test (DSST; WAIS-R)<br>• Digit Span Forwards and Backwards (WAIS-R)<br>• Continuous Performance Task (CPT)<br>• Reaction Time (RTI; CANTAB)<br>• Choice Reaction Time (CRT; CANTAB)<br>• Simple Reaction Time (SRT; CANTAB)<br>• Trail Making Test Part A (TMT A)<br>• Paced Auditory Serial Addition Test (PASAT)<br>• Serial sevens subtraction test (SSST) |
| **Working memory** | • Arithmetic (WAIS-R)<br>• Digit Span Forwards and Backwards (WAIS-R)<br>• Delayed Recognition Span Test (DRST)<br>• Spatial Working Memory (SWM; CANTAB)<br>• Letter-Number Sequencing (LNS; Wechsler Memory Scale Revised (WMS-R))<br>• Logical Memory (WMS-R)<br>• n-Back Test |
| **Verbal learning and memory** | • California Verbal Learning Test (CVLT)<br>• Rey Auditory Verbal Learning Test (RAVLT)<br>• Rivermead Behavioral Memory Test (RBMT)<br>• Hopkins Verbal Learning Test Revised (HVLT-R)<br>• Logical Memory (WMS-R)<br>• Verbal Paired Associates (VPA; WMS-R)<br>• Visual Verbal Learning Test (VVLT)<br>• Digit Span Forwards and Backwards (WAIS-R)<br>• Luria's verbal learning test (LVLT)<br>• SSST<br>• Verbal Recognition Memory Test (VRM; CANTAB) |
| **Visual learning and memory** | • Visual Reproduction (WMS-R)<br>• Benton Visual Retention Test (VRT)<br>• Benton Visual Form Discrimination (VFD)<br>• Rey-Osterrieth Complex Figure Test (ROCF)<br>• Kimura's Recurring Figures Test (RFT)<br>• Visual Verbal Learning Test (VVLT) |

Table 2.1 (*Continued*)

| Cognitive domain | Neurocognitive tests |
|---|---|
| | • Pattern Recognition Memory (PRM; CANTAB)<br>• Spatial Recognition Memory (SRM; CANTAB)<br>• Delayed Matching to Sample (DMS; CANTAB)<br>• Paired Associates Learning (PAL; CANTAB)<br>• Matching Familiar Figures Test 20 (MFFT-20) |
| **Language and verbal comprehension** | • COWAT<br>• Verbal, Category, and Letter Fluencies<br>• Similarities (WAIS-R)<br>• Vocabulary (WAIS-R)<br>• Information (WAIS-R)<br>• Comprehension (WAIS-R)<br>• Token Test |
| **Visuospatial/ perceptual processing** | • Judgement of Line Orientation (JOLO)<br>• Benton Visual Form Discrimination (VFD)<br>• Block Design (WAIS-R)<br>• Visuospatial Span Forwards and Backwards (WMS-R) |
| **Brief mental status** | • Mini-Mental State Exam (MMSE) |
| **General intelligence** | • Raven's Progressive Matrices<br>• WAIS-R<br>• National Adult Reading Test (NART)<br>• Wechsler Test of Adult Reading (WTAR)<br>• Test of Nonverbal Intelligence-3 (TONI-3) |
| **Cognitive battery** | • CANTAB<br>• WMS-R<br>• WAIS-R<br>• Victoria Symptom Validity Test (VSVT)<br>• California Computerised Assessment Package (CalCAP)<br>• Central nervous system (CNS) Vital Signs<br>• Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ)<br>• D-KEFS |
| **Psychomotor performance** | • Finger Tapping<br>• Grooved Pegboard Test<br>• Purdue Pegboard Test |
| **Decision making and response control** | • The Go/No-go Association Task (GNAT; CANTAB)<br>• Information Sampling Task (IST; CANTAB)<br>• Cambridge Gambling Task (CGT; CANTAB) |
| **Induction** | • Big/Little Circle (BLC; CANTAB) |

priority. Taken together, the hazards posed by cognitive deficits on functional outcome in individuals with MDD provide the impetus for refining disease models and extrapolating from the results reported in individuals with schizophrenia and BD. A consensus-driven development of measurement tools that can effectively detect cognitive decline in this population and batteries assessing cognitive deficits for both descriptive and interventional research is warranted.