# Quantifying Underlying Cognitive Processes

Precise evaluation of cognitive function can facilitate deep insight into overall brain health, which is affected by a variety of factors including normal aging, neurodegenerative disorders and their severity, pharmaco- and non-pharmacotherapies, and many others. As a framework for evaluating the directly observable aspects of cognition, the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM–5*) specifies 6 key cognitive domains (Figure 1),[1] each consisting of several subdomains. However, much deeper insight can be gained by characterizing underlying processes of encoding and retrieval that cannot be directly observed. Embic's quantified cognitive processes (qCPs) represent such underlying factors and enable more precise evaluation of cognitive health.
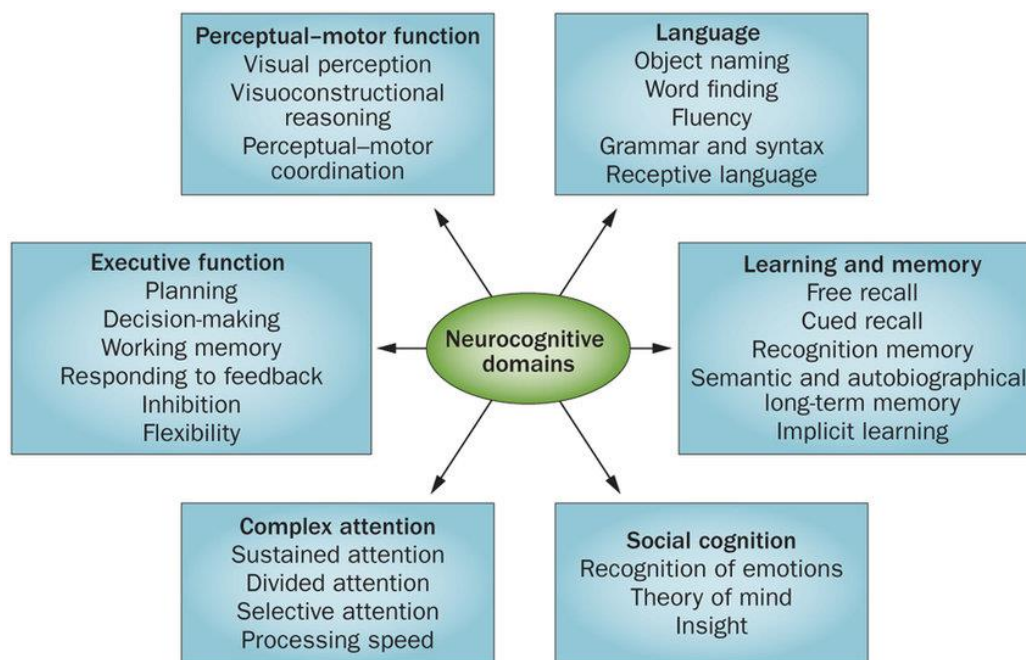

Figure 1. Six Key Cognitive Domains from the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM–5*). Excerpt from Sachdev et al.[1]

Over the past several decades, researchers have devised batteries of specific assessments aimed at testing these cognitive domains and subdomains (Figure 2). However, there is significant overlap among domains, which makes the evaluation of cognitive health complex and difficult to interpret, especially when cognitive changes are subtle or when deficits in specific domains can be masked by compensation in other domains. Recently, this challenge has led the field of neuropsychology to shift from traditional total and sub-scoring approaches used in assessments such as the MMSE, MoCA, Mini-Cog, Clock Drawing, CogState, RBANS, and SLUMS, to enhanced scoring methodologies using composite or weighted scores. Several newer assessment batteries including ADCS-PACC, ADCOMS, C3, feature such enhanced scoring approaches and optimize the utility of traditionally used assessment batteries.[2-6]

Despite these efforts, weighted and composite scores derived from traditional assessment batteries have critical limitations, because a small set of underlying processes animate multiple domains and affect performance in each of them. The process of encoding information into working memory and the

processes of storage and retrieval of information during delayed recall are prime examples of such underlying processes[7] that are shared across multiple domains. While characterizing these underlying cognitive processes provides a more granular and illuminating insight into overall brain health, they are not directly observable and are therefore difficult to quantify.
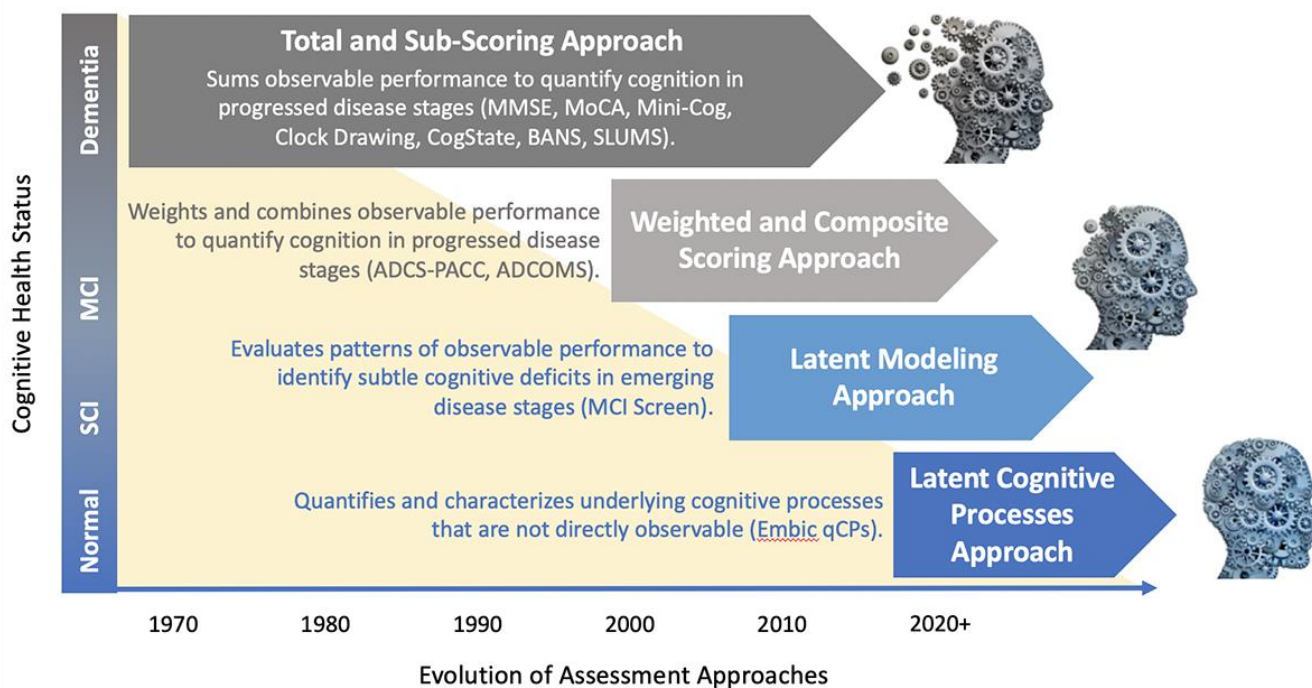
Figure 2. The Evolution of Enhanced Methods for Cognitive Assessment. Embic's qCPs quantify underlying cognitive processes that are unobservable and inaccessible with existing scoring approaches.

Quantified Cognitive Processes

Embic Corporation's qCPs quantify underlying cognitive processes of encoding and retrieval that cannot be directly observed and have been previously inaccessible. This scientific achievement was made possible by the combination of Embic's massive normative database of cognitively healthy adults, with a hierarchical Bayesian cognitive processing (HBCP) model, applied to item response data from commonly used wordlist learning, recall, and recognition tasks.[7]

The resulting qCPs enable a non-invasive and pragmatic approach to characterizing cognitive function at a granular level, which enables identification and quantification of very subtle cognitive changes. This capability facilitates a profound opportunity for accelerating and optimizing results in clinical trials, especially in the areas of cognitive aging and neurodegenerative diseases.

DEVELOPMENT AND VALIDATION OF QUANTIFIED COGNITIVE PROCESSES

Embic's qCPs are highly applicable in the field of Alzheimer's disease (AD). Insightful qCPs can be generated on item response data from most well-validated wordlist memory (WLM) tests and used to accomplish a wide range of research goals. Using item response data, qCPs are generated for underlying cognitive processes of encoding and retrieval that undergo clear and distinct changes throughout the course of AD. These qCPs quantify specific changes, even in pre-clinical stages of AD, the analysis of which facilitates identification of potential participants in early-stage AD drug trials and provides more granular insight about how cognition is affected as the disease emerges and progresses.

Several recent studies using Embic's qCPs are summarized below.

1. Generating Comparable qCPs Across Different WLM Tests

To evaluate the generalizability of qCPs across different WML tests, values were generated using item response data from 2,456 subjects who were assessed with three different WLM tests (i.e., ADAS-Cog, MCI Screen, or AVLT) and had diagnoses of cognitively normal, amnestic MCI, or AD dementia.[8] The changes in qCPs from normal to AD dementia were consistent across the three different WLM tests and data sources (Figure 3). The results demonstrate that these qCPs are robust and generalizable, regardless of the underlying test protocol, and allow comparison of various studies conducted using different WLM tests.
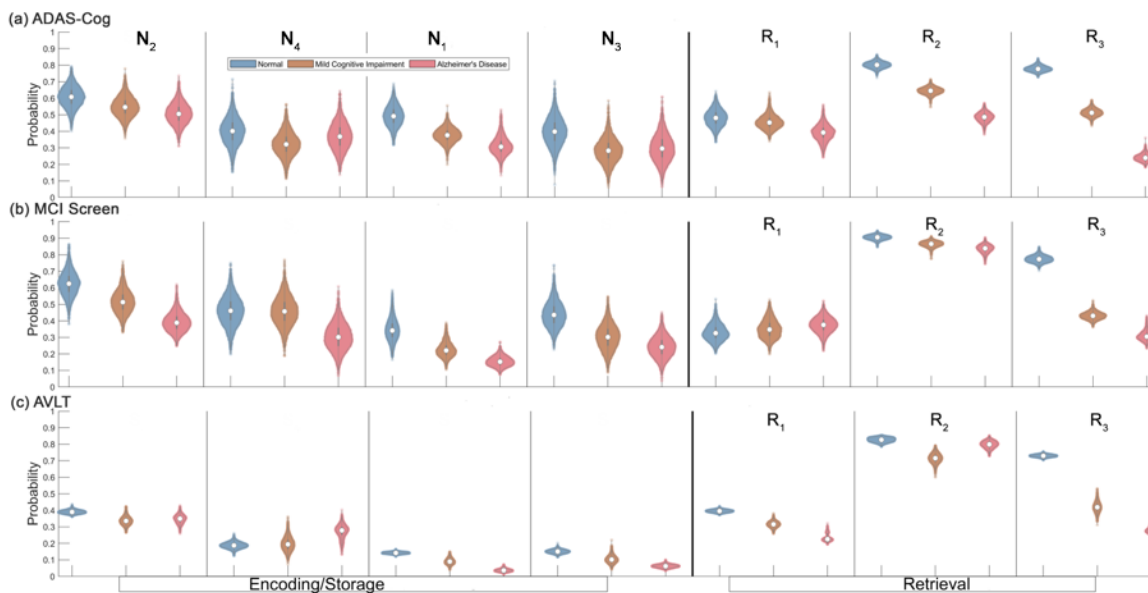

Figure 3. qCPs Across Three Different Wordlist Memory Tests. qCP parameters demonstrate consistent values and patterns of change across, ADAS-Cog, MCI Screen, AVLT wordlist memory testes, during the course of disease progression from normal, MCI, to AD dementia.

2. Detecting Cognitive Changes that Precede Perceptible Cognitive Decline in Subjects with AD

To evaluate the ability of qCPs to predict impending cognitive decline due to AD, values were generated from baseline assessments of 640 subjects who were assessed longitudinally with the AVLT WLM test in the Mayo Clinic Aging Registry. While all subjects were considered, according to best practice industry standards, to have normal cognitive function at baseline, the qCPs clearly distinguished the group who would maintain normal cognition (stable) from the group that would progress to aMCI or AD dementia (progressor) within three years.[9] This was further validated with baseline assessments of 503 subjects who were assessed with the ADAS-Cog WLM test in the Alzheimer's Disease Neuroimaging Initiative (ADNI).* The results showed, despite both stable and progressor groups being classified as cognitively healthy at baseline ADNI measurement, progressors already had measurable deficits in unobservable processes of encoding and retrieval (Figure 4).[10] These studies clearly demonstrate the ability of qCPs to pragmatically identify very early cognitive changes in subjects who are in the pre-symptomatic stages of AD. Furthermore, Embic's qCPs could potentially serve as important outcome measures in trials for therapies that effect cognition.
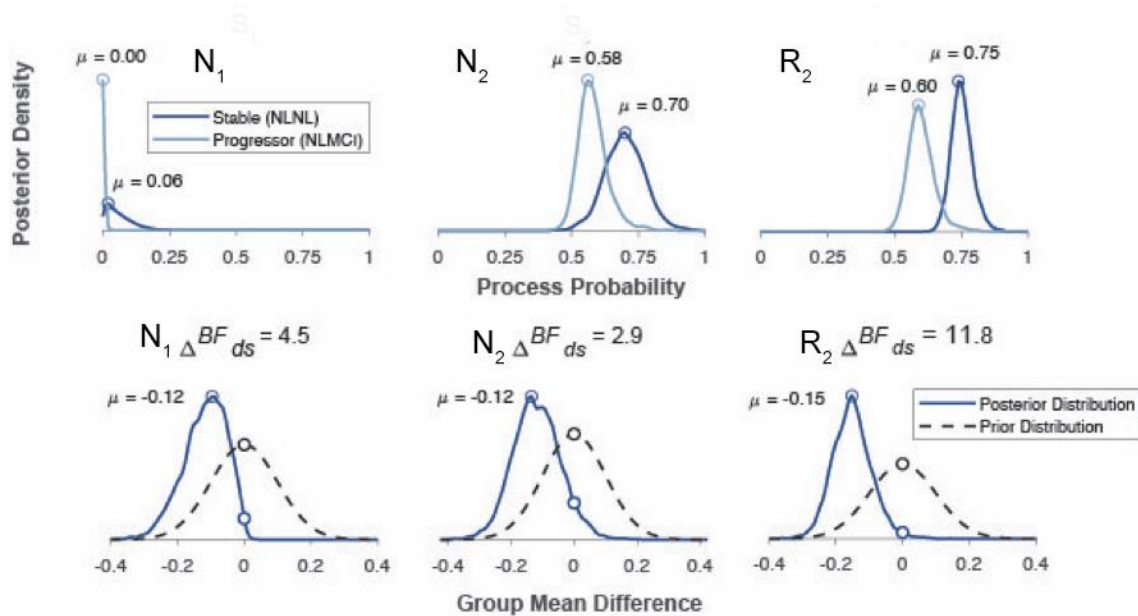
Figure 4. qCP Differences at Baseline for Stable vs. Progressor Groups. The progressor group showed clear decline in encoding and retrieval processes (N_1, N_2, R_2) at baseline.

3. Improving Prediction of Underlying Alzheimer's Pathology

To evaluate the ability of qCPs to predict underlying AD pathology, values were generated to establish predictive accuracy for subjects with known amyloid status according to CSF or PET measurement. This initial study was conducted using data from 200 randomly-sampled subjects who were assessed with the ADAS-Cog WML test as part of the ADNI study.[11] The results demonstrated that qCPs can distinguish the group with underlying AD pathology from the group without. Classification accuracy was better for CSF measurement, for MCI subjects than for cognitively normal subjects, and when including ApoE as a covariate (Table 1). Best PET measurement classification accuracy was found for MCI subjects when including ApoE as a covariate (.68). An on-going validation study will further improve this predictive capability of AD pathology, enabling a non-invasive and cost-effective approach to pre-screening study subjects prior to more invasive and costlier PET or CSF studies.

**Table 1**. Classification Summary of ADNI CSF Amyloid

Stage	NL		MCI	
Sample (Amyloid + / Amyloid -)	19 / 31	19 / 31	31 / 19	31 / 19
ApoE Status Included	N	Y	N	Y
HBCP Parameters Used	*r, t*	*r, t*	*t, L2*	*t, L2*
PPV	0.78	0.79	0.70	0.82
NPV	0.96	1.00	0.48	1.00
Accuracy	0.88	0.90	0.60	0.86

These qCPs allow better identification and characterization of AD patients while in the pre-symptomatic or mild cognitive impairment stages of disease progression, which will enable pragmatic screening and more efficient enrollment for AD clinical trials. This capability can also serve as an important tool for the timely identification of patients with emerging AD pathology as disease-modifying therapies become increasingly available.

QUANTIFYING UNDERLYING COGNITIVE PROCESSES

Embic's proprietary algorithms use item-level response data from widely-adopted neuropsychological tests to generate qCPs. These qCPs have been validated through ongoing research & development efforts, including those funded by the US National Institutes of Health in collaboration with leading academic institutions in the area of AD and overall brain health across the human life span.

Embic's qCPs are derived through a sophisticated process that draws on the strengths of the company's intellectual property and is grounded in well-established neuropsychological theory (Figure 5). The mathematical models that generate the qCPs are constructed using proprietary algorithms based on hierarchical Bayesian modeling and multinomial processing trees. Data are evaluated at the item level to capture serial position effects in a given task's presentation protocol and conditional response patterns that facilitate the most robust characterization of cognitive performance. Additionally, the company's proprietary dataset of nearly two million completed assessments (using wordlist memory and recognition tasks) provides insightful normative references for how healthy adults perform across the human life span. These data infuse our cognitive models with a higher degree of precision.
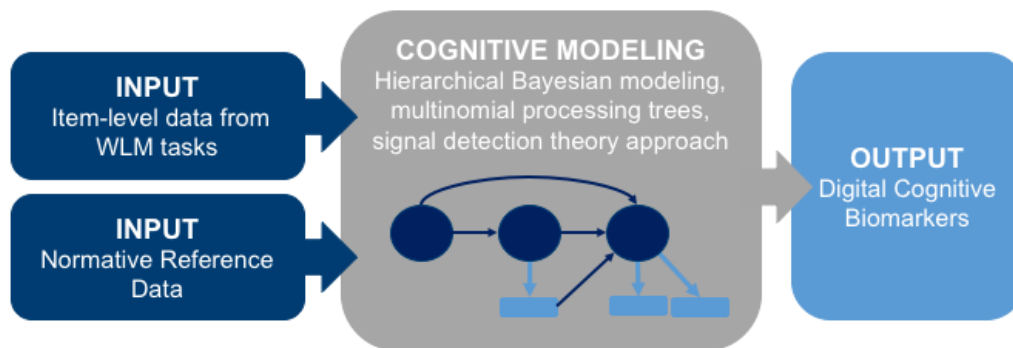
Figure 5. Embic's Approach. Item level responses to wordlist memory and recognition tasks are combined with normative reference data and analyzed with carefully selected algorithms to generate qCPs that quantify an individual's underlying processes for encoding and retrieving information.

Leveraging Item-Level Response Data as Input Data

Commonly used and well-validated cognitive assessment tasks, such as wordlist learning and recognition tests, collect a vast amount of data that contain valuable signals about cognitive function. These signals, however, cannot be isolated using traditional scoring approaches that rely heavily on summary scores or weighted composite calculations [Bock 2020]. Embic's scoring approach uses well-established cognitive models that extract the patterns of information contained in item-level response data and quantifies them as qCPs. These qCPs are therefore the quantification of unobservable cognitive processes, including encoding and retrieval, that enable deep insight into overall cognitive health.

Incorporating Normative Reference Data

Embic's models have been refined using neuropsychological performance norms derived from a growing database of nearly two million proprietary assessments. This massive normative database yields informative *priors,* computed for each combination of gender, education, and age across the entire adult lifespan. These priors improve the precision of Embic's cognitive models by enabling a better understanding of each individual's cognitive performance relative to a healthy pool of subjects in their demographic peer group.

Developing Cognitive Process Models

Embic's cognitive models have been developed using sophisticated mathematical methods such as hierarchical Bayesian analysis and multinomial processing tree modeling. These methods have been widely used in many fields of science and are well validated with extensive empirical evidence. They

are ideally suited to the challenge of quantifying the unobservable cognitive processes used in learning and recalling new information (Figure 6).
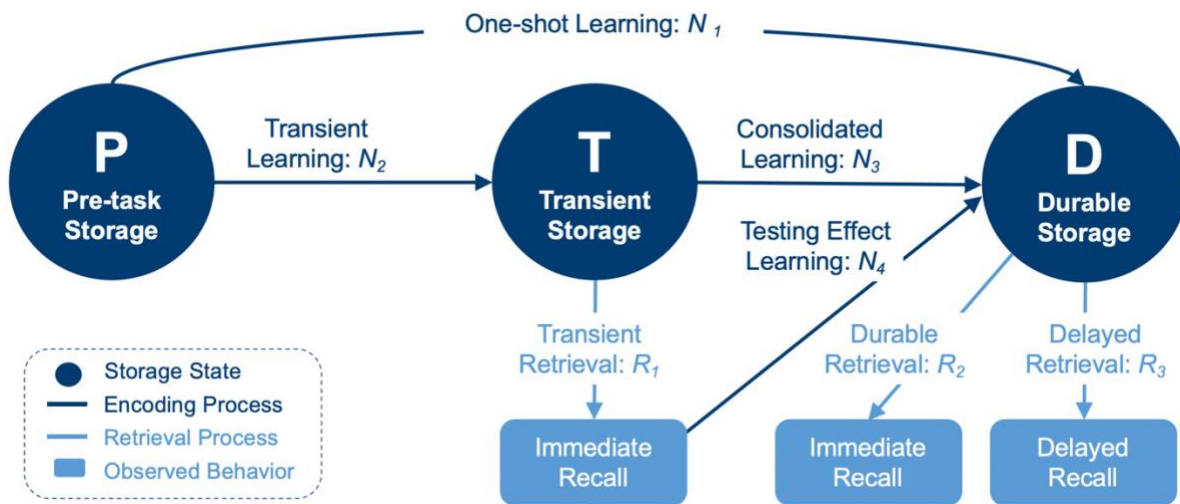
Figure 6. Hierarchical Bayesian cognitive Processing Model. The model has three episodic memory storage states (P, T, and D), four processes of encoding among them (N_1, N_2, N_3, and N_4), and three processes of retrieval from them (R_1, R_2, and R_3).

SUMMARY

Over the past twenty years, Embic Corporation has assembled a normative dataset of cognitive performance from nearly two million normally aging adults. Combining the company's broad domain knowledge of cognition and application of mathematically sophisticated cognitive models, Embic has leveraged the information contained in this massive dataset to develop a library of insightful qCPs. The company's innovative approach to characterizing and quantifying underlying cognitive processes has illuminated aspects of brain health that have been previously inaccessible. Embic's qCPs have been validated through collaborations with academic institutions, journal publications, NIH grant funding, and industry adoption. These qCPs have been recently approved for inclusion in the ADNI database, the most comprehensive source of Alzheimer's research data in the world.

As the world's population ages, there is an urgent need to proactively manage cognitive health. Doing so will require ongoing advances in the evaluation and characterization of underlying cognitive processes and how they are affected by aging, disease progression, therapeutic interventions, and other environmental factors. Embic's qCPs provide invaluable insight that will facilitate and accelerate improvements in research and care delivery for an aging population at risk of declining cognitive health.

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