

**The National Institutes of Health
National Institute of Nursing Research
Working Group on Promoting Research on Focal Cognitive Deficits
in Non-Dementing Disorders
Bethesda, MD
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EXECUTIVE SUMMARY

Diseases of the central nervous system (CNS) are among the most physically and mentally disabling conditions. It is estimated that as much as 5 percent of the adult population in the United States may live with non-dementing brain disorders. Dementing disorders cause global cognitive deficits and are generally thought to be progressive. Conversely, non-dementing disorders affect one or more targeted or focal cognitive functions while leaving others intact. Examples of non-dementing neurological conditions include degenerative conditions such as multiple sclerosis (MS), epilepsy, Parkinson disease, amyotrophic lateral sclerosis; congenital abnormalities such as cerebral palsy; and event-induced disorders such as stroke. Additional examples include migraine disorders, sleep disorders such as sleep apnea and insomnia, spinal cord injury, tic disorders such as Tourette syndrome, sensory disorders such as Meneire syndrome, ataxias such as Friedreich ataxia, and communication disorders such as expressive aphasia.

In assessing the burden of these chronic neurological conditions, little or no research has addressed the secondary effects of decreased cognitive and affective function on patients' physical health and quality of life (QoL). The limited existing data suggest that these conditions can cause focal cognitive deficits affecting a range of function areas, which may impair decision-making, alter psychosocial functioning, and reduce productivity. Research suggests that non-demented individuals with reduced cognitive function do not participate fully in health-seeking and health-maintaining behaviors.

Implicit in the definition of non-dementing disorders is the existence of targets for intervention and the presence of sufficient neurofunctional reserve to make it possible to engage in and benefit from treatment. Because of the extent of available cognitive research, intervention for these individuals appears possible. Though a significant body of research exists on dementing conditions like aphasia and Alzheimer disease, considerably less is known about milder conditions, presenting an opportunity to move the current science forward. In addition, although there is limited opportunity for significant and sustained impact when intervening in global, severe conditions, there exists a window of opportunity to enhance QoL in individuals experiencing mild to moderate focal cognitive deficits, who are often excluded from intervention activities because their deficits are not considered severe enough. There is a need to uncover and understand the extent to which these mild and moderate deficits affect functional outcomes and to understand what these cognitive changes mean at the levels of the individual, family, and greater society. A host of scientists and clinicians from multiple disciplines, including nursing, neurology, psychology, psychiatry, occupational therapy, and rehabilitation sciences are involved in researching various aspects of cognitive impairment in non-dementing CNS disorders.

To explore the current state of research, identify gaps in understanding, highlight challenges in the field, and determine opportunities to advance the science of focal cognitive deficits in non-dementing disorders, a working group of research scientists convened for a 1-day meeting organized by the National Institute for Nursing Research (NINR), with partial support from the NIH Office of Rare Diseases. The working group was charged with addressing four objectives: 1) to highlight current knowledge of focal cognitive changes observed in non-dementing CNS disorders and their effects on QoL, health behaviors/health decision-making, and health outcomes; 2) to identify current research gaps in the knowledge base of focal cognitive changes observed in non-dementing CNS disorders and their effects on QoL and health outcomes; 3) to define challenges and emerging opportunities for research in this area; and 4) to identify areas of opportunity for research in affected populations. The deliberations of the working group are intended to assist program staff in the consideration of a research agenda related to improving health and QoL outcomes for persons with brain disorders, and to developing effective pharmacotherapy and cognitive-behavioral interventions that will reduce cognitive deficits and promote better health behaviors and health decision-making.

Presentations and discussions provided platforms for reviewing ongoing research, including challenges in study and intervention design, and recommendations for future research in the area. One presentation outlining focal changes in cognitive functions in non-dementing conditions provided the framework for the day's discussion. Another presentation on the methodological issues of research on cognitive change explored barriers and promising approaches regarding design, measurement, and sampling. This presentation challenged the assumption that focal deficits can be identified by differential or interaction analyses, and underscored the need for evidence of statistically distinct influences that distinguishes among retest effects, within-person variability, and between-person variability. Other presentations highlighted the existing research and knowledge gaps in measuring and understanding the impact of cognitive impairments in persons affected by epilepsy, MS, and stroke. An overview of existing evidence-based treatments and methodological challenges provided a clearer picture of future directions for intervention research. A final brainstorming activity allowed the group to suggest areas for further research needed to advance understanding of focal cognitive deficits in non-dementing CNS disorders. A particular emphasis was placed on the development and implementation of promising interventions.

Current State of Research

Evidence suggests that drug, training, and rehabilitation interventions can improve cognitive functioning in individuals with non-dementing disorders experiencing focal cognitive deficits. However, "one-size-fits-all" approaches to intervention are not effective in this population, as multiple individual characteristics significantly influence intervention outcomes. Training effects for some behavioral interventions are reasonably durable for particular individuals but not guaranteed to persist and not always generalizable. As a result, many different intervention models and methods are needed to facilitate cognitive and functional maintenance and improvement across a variety of diseases, cognitive deficits, and behaviors for the diverse group of patients in need of interventions. Though there is evidence of immediate effectiveness and short-term maintenance of behavior changes from interventions, few studies have examined the

potential for long-term maintenance of rehabilitative health behaviors in the population of interest.

It appears that there are cognitive changes that are common across non-dementing disorders including, but not limited to, aspects of memory function, language control, attentional control, fatigue, and pain. In order to understand disease-specific issues, as well as cognitive deficits across diseases, it is important to consider the heterogeneity of disease experiences while including population groups that are homogenous with respect to, for example, type of cognitive deficit, severity of cognitive deficit, profile of cognitive strengths and weaknesses, and underlying cause(s) of deficit. Emphasis also has been placed on the use of a variety of measurement techniques.

Defining the intended population of study is a challenge for intervention research that concentrates on focal cognitive deficits because these deficits occur within a continuum of cognitive function, ranging from no deficit to dementia/global cognitive deficits. Adding to the challenge is the complexity associated with the interaction of brain regions in the execution of a given task. In order to address this, the working group defined the term “cognitive deficits in a non-dementing disorder” as follows: a CNS disorder that can occur at any time across the lifespan with slowly or non-progressive focal cognitive impairment that affects social and occupational performance at the individual level, but is associated with sufficient cognitive reserve that the individual can engage in and benefit from treatment without the underlying medical disorder rapidly erasing the benefits of the treatment.

The field has a variety of assessments available to measure cognitive outcomes. Less is known, however, about the measurement of functional outcomes among non-demented individuals with focal cognitive deficits, even though the latter is of great importance to patients. The development of more sensitive and specific measures for the field would improve understanding of the incidence and prevalence of mild and moderate cognitive impairment, the cognitive and functional outcomes of these impairments, and the effectiveness of interventions designed to enhance functioning and improve QoL.

Currently there are multiple accepted avenues for intervention: target cognitive variables that underlie everyday performance and mediate functional activity, requiring an in-depth understanding of the mechanisms underlying the impairment; directly address the functional variable, often through behavioral interventions targeting a particular activity; solicit patient input to develop a self-shaping intervention, where the patient determines the relevant areas or priorities for intervention. It is clear that no one single approach will be effective for everyone and that individual characteristics significantly influence intervention outcomes. As a result, many different intervention models and methods will be needed to facilitate cognitive and functional change for the affected population.

Much of the current knowledge about focal cognitive impairment in non-dementing disorders has been derived from small-group or single-case studies. This is perhaps related to the relatively low incidence and prevalence of some of the disorders found in the non-dementing disease category. The absence of appropriate comparison groups is a major challenge for understanding focal cognitive impairments among non-demented individuals and the effects of these

impairments on cognitive and functional outcomes. Thus, there is very limited evidence appropriate for generalization. To facilitate cross-group or cross-study comparisons, there must be some agreement on a set of accepted measures of cognitive and functional outcomes.

In general, the field has progressed rather slowly because of methodological limitations. Steps that would contribute to the advancement of appropriate and effective intervention testing include: defining affected populations, interventions, and outcomes (e.g., mild cognitive impairments, fatigue, pain) more clearly; measuring interventions in ways that are relevant to the individuals being treated; and conducting adequately powered studies to assure the detection of meaningful clinical impact, and that reference an appropriate non-clinical comparison group. Researchers in the area are poised for the development and testing of reproducible interventions that will significantly affect patients' ability to interact with their environment and will be incorporated as standard of care for those individuals experiencing mild to moderate deficits associated with non-dementing conditions.

Recommended Research Areas

The working group suggested a number of areas for further research on focal cognitive deficits in non-dementing disorders. Though the articulated main goal for research is developing effective cognitive-behavioral and psychosocial interventions for the population of interest, there is agreement that intermediate research areas must be addressed, including understanding underlying mechanisms of impairment and developing appropriate measures that will advance intervention development and capability. These recommendations can be grouped into three broad areas as follows.

Basic Research, Underlying Mechanisms, and Interventions

- Identify and characterize cognitive impairments, including their incidence and prevalence, subtypes, as well as screening techniques.
- Establish and/or uncover linkages between pathology of the impairment and actual impact on people's lives.
- Improve understanding of brain mechanisms underlying cognitive deficits and implications for everyday performance.
- Examine linkages between cognitive impairment and self management.
- Determine predictors of treatment response.
- Improve understanding of mechanisms and mediators of treatment intervention effects.
- Analyze specific elements of interventions to better understand the specific contributors to treatment effect, including timing, dose, and schedule.
- Characterize potentiators of cognitive interventions including physical activity, biofeedback, imagery, pre-training activities, motivational enhancement, drugs, complementary and alternative medicine (CAM), family environment, and/or caregiver involvement.
- Identify maladaptive techniques and other internal obstacles that perpetuate unhelpful outcomes in order to effectively direct interventions (i.e., "untraining" or deprogramming).
- Describe cognitive deficits in less studied groups, such as the elderly, adults who are non-surgical candidates, children, and community samples of children and adults.

- Systematically compare combinations of different interventions and intervention approaches.
- Conduct studies of cognitive constructs compared across diseases (commonality versus differences, effects on nature, and treatment across diseases).
- Develop and compare new treatment approaches.

Methods and Measurement

- Develop an accepted core set of measures reflective of certain functions/abilities while at the same time allowing for greater specification.
- Develop new sensitive and specific measures, particularly in the area of functional outcome and everyday life.
- Identify and develop multiple objective measures of outcome, including disease-specific economic and societal (e.g. cost effectiveness, utilization of services) outcome measures.
- Match treatment approaches to different populations.
- Utilize technology to measure intervention impact, such as personal digital assistants (PDAs), the Internet, and telephone, as well as functional neuroimaging.
- Improve implementation of treatment trials and develop novel training methods for interventions, such as trainerless training that relies on interactive groups, online learning, CD-ROM-based training, and multimodal approaches.
- Aggregate datasets with overlapping measures to increase sample size and create opportunities for more powerful analyses not possible with the smaller sample sizes typical in the study of focal deficits.

Translation of Research

- Disseminate and translate effective intervention research findings into widespread clinical practice, with consideration given to relative ease of reproducibility and cost-effectiveness.
- Support studies that can generalize interventions to real-world functions in both activities and settings and to non-trained cognitive functions, including reproducibility.