Call to Arms for Perioperative Cognitive Medicine Specialists

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Our healthcare system faces an extensive gap in evidence-based perioperative care for adults with Alzheimer's Disease (AD) and related dementias and other progressive neurodegenerative disorders (e.g., Parkinson's Disease). This is particularly concerning because at least 20% of older patients undergoing surgery have undiagnosed dementia (Amini et al., 2019a; Culley et al., 2016), and individuals with neurodegenerative disease will arrive at preoperative anesthesia centers in exponentially larger numbers over the next 25 to 50 years. By 2050, people aged 65 and older will reach 1.6 billion worldwide (He, Goodkind, & Kowal, 2016). Our healthcare system will face larger numbers of individuals with early to late stage AD(Hebert, Scherr, Bienias, Bennett, & Evans, 2003) and other neurodegenerative disorders needing procedures with anesthesia due to serious health related conditions (e.g., cardiac) and desire for quality of life improvement surgeries (e.g., joint replacement) (Williams, Wolford, & Bercovitz, 2015). Despite this, healthcare professionals within the perioperative setting typically know very little about neurodegenerative type, severity (measured by pathology, neuroimaging, or cognition), or neurodegenerative pharmaceuticals interactions with anesthesia agents (Aminoff et al., 2011).

Currently, patients with AD and other neurodegenerative disorders receive comparable perioperative care to that of their cognitively-intact counterparts (Silbert, Evered, & Scott, 2011). Patient-centric needs are not often proactively considered. Population and healthcare trends dictate an urgent need for an integrated approach to perioperative research for AD and related dementias. There is a unique need for clinical psychologists and particularly board certified with neuropsychology specialists with expertise in neurodegenerative disorders, pre to postoperative cognitive change, and delirium to: 1) create perioperative cognitive clinics within pre-surgical anesthesia centers; 2) provide tailored recommendations to patients and medical provider; 3) develop evidenced-based research addressing brain-behavioral profiles, neurodegenerative diseases, and anesthesia and surgical interactions.

Some reasons why:

Reason 1: Despite studying cognitive change after general surgeries with anesthesia and also delirium for over 70 years (Bedford, 1955), there are no known surgical or anesthetic mechanisms for cognitive complications. General anesthesia remains an unconfirmed influence on cognitive decline per randomized studies (Rasmussen et al., 2005; Somprakit et al., 2002; Williams-Russo, Sharrock, Mattis, Szatrowski, & Charlson, 1995) and large database analyses (Kline et al., 2012; Perucho et al.; Sprung et al., 2016). This is surprising given the numerous animal studies suggesting that inhalational anesthetics enhance oligomerization and cytotoxicity of amyloid β

peptides (a protein change associated with Alzheimer's Disease, (Perucho et al.), tau phosphorylation (Le Freche et al.), and associated neuro-inflammatory response in humans (Tang et al., 2011). Surgery-related mechanisms of postoperative cognitive dysfunction also remain inconclusive. For example, in total knee arthroplasty, tourniquet time has been hypothesized to be associated with increased embolic events and complications, but results show trends at best. In cardiac surgeries, the role of postulated surgical mechanisms such as cerebral embolic load, alterations in cerebral blood flow, core-periphery temperature gradients, and other issues related to cardiopulmonary bypass on post-operative cognitive dysfunction also remains controversial (Lund et al., 2005; M. F. Newman et al., 1995; Selnes, McKhann, Borowicz, & Grega, 2006; Tuman, McCarthy, Najafi, & Ivankovich, 1992).

Reason 2: There is resounding evidence that pre-operative cognitive characteristics are significant predictors for post-operative cognitive complications including later cognitive change, delirium, and mortality after elective surgical procedures. Increased age is a risk for cognitive decline after non-cardiac (Moller et al., 1998; Monk et al., 2008) and cardiac surgeries, with at least 10-15% of prospective study participants >65 years old experiencing cognitive decline at three months after surgery. Aside from age, lower education is a repeatedly established risk for postoperative cognitive change (Moller et al., 1998; Monk et al., 2008) with higher education and better outcome attributed to better preoperative brain status (greater cognitive reserve), better test-taking abilities, and the interrelationships between educational advancement, social support, and better postoperative medical care. Other published risk factors include lower preoperative executive function(Greene et al., 2009; Price, Garvan, Hizel, Lopez, & Billings, 2017), higher rates of pre-surgical depression (Greene et al., 2009; Price, Pereira, et al., 2015; Smith, Attix, Weldon, Greene, & Monk, 2009), frailty (H. S. Lin, Watts, Peel, & Hubbard, 2016), and pre-surgical evidence of a non-symptomatic stroke (Giovannetti et al., 2019; Goto et al., 2001). Nuances of pre-operative human brain function and behaviors deserve greater attention by our professionals. To date, the majority of the research addressing the role of preoperative cognition on outcome has been conducted by anesthesiology or surgeons. Yet, the cognitive and psychosocial aspects of these strongly established risk factors remain beyond the traditional scope of research and practice amongst anesthesiologists, thereby necessitating enhanced collaborations with neuropsychology and health psychologists. It is time neuropsychologists assist our collaborators in the anesthesia and surgical fields.

Reason 3: Baseline preoperative cognition is reduced in substantial sets of pre-surgical patients. Up to a fourth of community dwelling individuals present to a preoperative setting with early signs of mild neurocognitive disorder (Luck et al., 2017). Cognitive impairment has been shown through prospective investigations with screening tests (Amini et al., 2019b; Culley & Crosby, 2016; Culley et al., 2016) and in large prospective studies of patients being followed for post-operative outcome e.g., (Giovannetti et al., 2019). However, it remains unclear how the distribution and characterization of such baseline cognitive impairment is associated with the distribution of other important perioperative patient characteristics such as comorbidity status, health literacy, and global functioning. We do know preoperative cognitive impairment is associated with failure to arrive at scheduled procedures (Arias et al., 2019), increased use of emergency and rehabilitation services (de Gelder et al., 2018), prolonged hospitalization and complications (Culley et al., 2017; Fick, Kolanowski, Waller, & Inouye, 2005). Failure to identify cognitive vulnerabilities increases costs and negatively impacts benefits associated with necessary procedures. Insight into cognitive status within preoperative anesthesia settings will identify need for prehabilitation, additional preparatory planning support, and increase perioperative monitoring (Calkins, 2018; Mohanty et al., 2016; Prizer & Zimmerman, 2018). Discussions on pre-existing cognitive vulnerabilities help patient-caregiver dyads make informed healthcare decisions (Arias, Bursian, Sappenfield, & Price, 2018)

Reason 4: Patients with AD and related dementias as well as other neurodegenerative disorders such as Parkinson's disease (PD) have greater risks in perioperative settings (Aminoff et al.), and neuropsychologists are uniquely poised to identify undiagnosed characteristics of these disorders in a preoperative environment. Cognitive and psychiatric deficiencies associated with dementia interfere with a patient's ability to comply with medical recommendations and navigate complex environments independently (Ala et al., 2018). Cholinergic

system response to anesthesia (Pratico et al., 2005) and inflammation responses (Whittington, Planel, & Terrando, 2017) are hypothesized to be atypical for individuals with AD (Baranov et al., 2009; Silbert, Evered, Scott, & Maruff, 2011) as well as PD (Bohnen & Albin, 2011). Retrospective studies and single case reports show that individuals with neurodegenerative disorders such as Parkinson's disease have greater rates of postoperative delirium and cognitive decline (J. M. Newman et al., 2018). Nevertheless, patients with AD and other neurodegenerative disorders receive preoperative care which is comparable to their cognitively-intact counterparts, not taking into account their special needs (Silbert, Evered, Scott, et al., 2011). Retrospective studies and single case reports show that individuals with neurodegenerative disorders such as Parkinson's disease have greater rates of postoperative delirium and cognitive decline (J. M. Newman et al., 2018). There are few prospective human longitudinal studies involving patients who meet criteria for AD or related dementias (Eckenhoff & Laudansky, 2013). One factor is the many challenges with prospective recruitment of surgical patients with AD or other disorders for research studies (Price, Levy, et al., 2015). Anesthesiologists and surgeons are not trained to recognize these special considerations surrounding perioperative cognitive care for patients with neurodegenerative diseases. For these reasons, the benefit/risk ratio for procedures are misrepresented to patients with compromised cognition; precluding informed decision-making and inadequate risk identification of the potential for surgical anesthesia to exacerbate neurodegeneration. (Arora, Gooch, & Garcia, 2014). Consequently, there has been a call to action for preoperative identification of patients with AD and related dementias, improved understanding of brain mechanisms of change, and intervention options (Crosby, Culley, & Hyman, 2011). Board-certified neuropsychologists understand neurodegenerative disorders, their associated neurochemical disruptions, potential medication interactions, frailty patterns, vascular risk profiles. Neuropsychologists are therefore the appropriate peers to work with anesthesiology, surgery, and hospital administration to address perioperative cognitive care planning. If our disciplines develop integrated anesthesiology-neuropsychology-geriatric teams such as those at some major universities, then largescale multicenter prospective clinical research addressing surgical-anesthesia risk for individuals will be feasible.

Reason 5: Post-operative cognitive, delirium, and brain profiles appear to vary based on preoperative brain profile. Individuals can exhibit isolated post-operative memory impairment (55%), isolated executive impairment (33%), and 'combined' impairment (12%) despite performance of ADL's at a level that may mask preliminary stages of functional impairment (Price, Garvan, & Monk, 2008). Results suggest that clinicians can expect at least 15% of their older adult non-cardiac surgery patients to experience at least mild postoperative memory disturbances (1 standard deviation decline from baseline), with approximately 11% of all patients experiencing executive problems alone or in combination with memory problems. These findings have been replicated (Price et al., 2014) and indicate individuals can have different neuroanatomical regions of vulnerability. This fits with our understanding of brain & behavioral vulnerabilities and the threshold effect (Satz, 1993). Preoperative cognitive and brain vulnerabilities also predict intraoperative responses and acute pre to post-operative functional and microstructural changes. Preoperative cognitive reserve and brain integrity (e.g., reduced entorhinal thickness, more white matter disease, large ventricular size) predict differences in intraoperative anesthesia brain EEG responses(Giattino et al., 2017; Hernaiz Alonso et al., 2019) and pre-post brain functional and structural changes (Browndyke et al., 2017; Hardcastle et al., 2019; Huang et al., 2018; Tanner et al., 2019).

Reason 6: Anesthesia providers have growing awareness regarding the value of cognitive assessment in the preoperative setting. Although in 2013 the United States Preventive Services Task Force (USPSTF) refrained from recommending routine screening for cognitive impairment (citing stress related to misdiagnosis and the absence of efficacious treatment to mitigate cognitive decline may reduce the potential benefits associated with early detection of dementia) (J. S. Lin, O'Connor, Rossom, Perdue, & Eckstrom, 2013); the new 2019 American College of Surgeons Geriatric Surgery Verification (ACS GSV) Program (Surgeons, 2019) strongly recommends preoperative and postoperative cognitive and functional status screening for older adults electing surgery. The ACS GSV Program also recommends that the cognitive screener completed preoperatively should also be administered post-operatively. Cognitive screening documents should then be attached to medical records

for geriatric interdisciplinary care teams. Based on these recommendations and the plethora of growing data showing the value of cognitive screening in older adults, medical teams are now faced with the dilemma of which measure to choose and how to appropriately use them in the clinical setting. Colleagues in the American Society of Anesthesiology (ASA) and the International Anesthesia Research Society (IARS) are asking for collaboration with neuropsychologists to promoting brain health before, during, and after surgery. Anesthesiologists have pushed the concept of a 'perioperative home' for patient care and have a strong record of team science. There is a clear desire for collaboration from our medical colleagues. It is now our time – as neuropsychologists – to bridge the gap with anesthesiology and surgery to address brain-anesthesia interactions. The bottom line: The field of perioperative medicine needs clinical psychologists and particularly those with neuropsychological and health psychology expertise. These disciplines understand brain-behavioral, cognitive-behavioral nuances, neuroanatomy, neuroscience, and psychological disorders. More importantly we are invested in preserving brain-behavioral function. This potential capitalizes upon neuropsychology's existing foundation with peri-surgical epilepsy, movement disorder (deep brain stimulation), and brain-tumor mapping programs. We are consequently uniquely poised to provide useful recommendations to providers for intraoperative and post-operative considerations, and develop evidence based perioperative interventional approaches particularly for patients with neurodegenerative disorders needing/electing surgical procedures with anesthesia. The neuropsychology specialty is perfectly positioned to work with geriatric medicine to co-lead clinical and research endeavors for patients and healthcare systems. New frontiers await with specialty development of perioperative cognitive medicine. With our perioperative medical colleagues we can tackle complex topics that will be increasingly problematic in the years to come.

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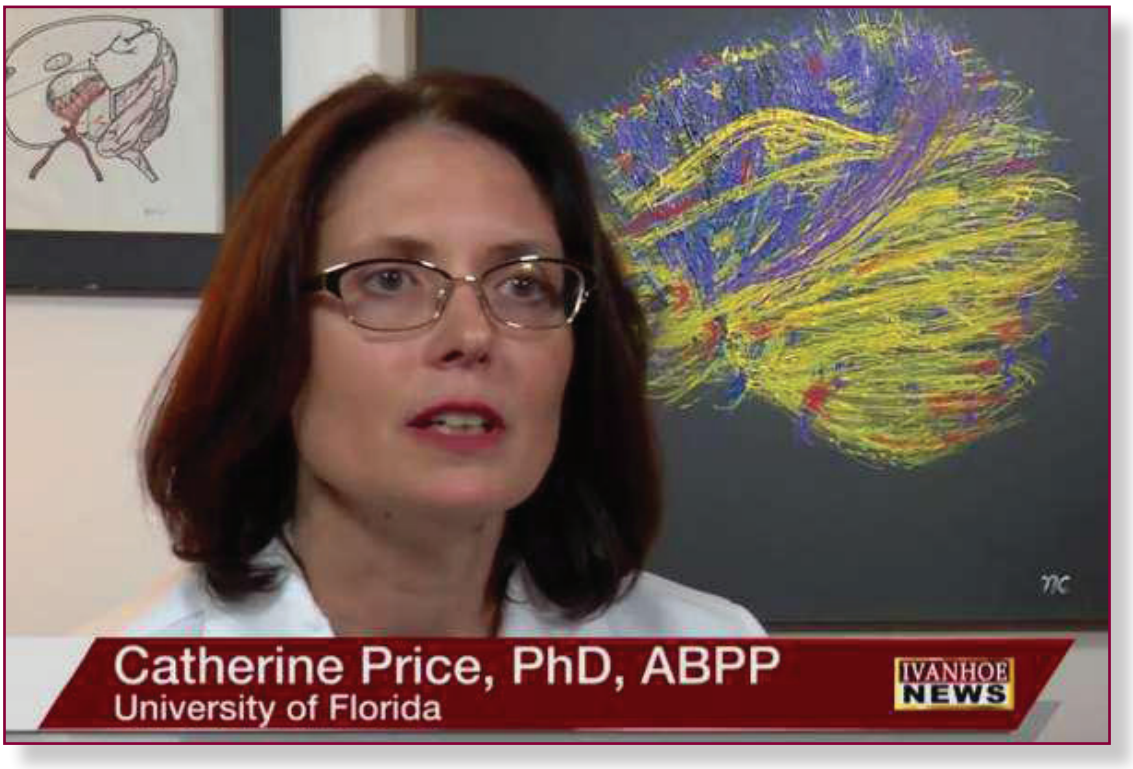

Dr. Catherine Price is board certified clinical psychologist with specialty in neuropsychology. Her academic goal has been to address the intersection of neuropsychology, neuroimaging, and cognitive change either due to neurodegenerative disorder acceleration or insults from medical interventions (such as elective surgeries with anesthesia). Her career developed in a series of stepping-stones. First, she states she garnered foundational expertise on brain-behavioral concepts. Next, she immersed myself in a number of endeavors: 1) research addressing cognitive profiles in common neurodegenerative disorders; 2) expertise development in cognitive-neuroimaging applications; 3) focused research on white-gray matter disease interactions for mild cognitive impairment, Alzheimer's Disease-vascular dementia spectrum profiles, and Parkinson's Disease; 4) focused prospective research on older adult brain-behavioral changes after surgical/anesthesia exposure; and 5) research into digital neuropsychological applications for early disease recognition. Now she is targeting clinical-research addressing larger public health related questions on older adult cognition and neurodegenerative disease prevalence in the preoperative setting, and neuroimaging/biomarker brain burden risk profiles for negative postoperative cognitive complications. She has had three NIH R01s and she is the recent recipient of a NIH five year academic leadership award to develop the Perioperative Cognitive Anesthesia Network research-clinical-training program for Alzheimer's Disease and related dementias.