Plasticity and Brain Aging

U13 Bench-to-Bedside Conference
“Sensory Impairment and Cognitive Decline”

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GAPS of studies on brain plasticity and aging:
--Limited information on underlying age-related CNS changes
--Healthy and high functioning young old

Do these matter?
REVISITED FOCUS: age-related CNS changes
- can drive functional decline either directly or by weakening the potential for plasticity.

Next slides: examples of age-related CNS characteristics that have recently emerged with advanced neuroimaging technologies.

Focus: structure of gray and white matter and vessels.
Example 1: dormant neurogenesis

a) Ultra-high field imaging: in vivo “dissection” of hippocampal formation into its subregions.
---Dentate gyrus: neuroregenerative potential.
----Cornu ammonis: Vulnerable to ischemia, stress; atrophy predates cognitive impairment.
- Rodent/ non human primates

b) Experimental/proofof concept studies: PA, transcranial MRI-guided focused ultrasound.

RESEARCH OPPORTUNITIES:
- Underlying mechanisms (new neurons, viable, richer dendritic arborizations, more blood)
Example 2: small arteries and veins

a) Time of flight, ultra-high field susceptibility weighted images: direct visualization of small arteries and veins w/out contrast. # and tortuosity.

b) Small veins’ tortuosity/lower arterial density: AD, APOe4, Physical activity

RESEARCH OPPORTUNITIES
-- mechanisms (inefficient angiogenesis?)
- Few studies
- small N

Bouvy, 2017 JAD

A: Tortuosity ratio = 0.68
B: Tortuosity ratio = 7.03

Shabaan, AJNR 2017

Normalized Vessel Count

Bullitt, NBA, 2010
Example 3: microstructure of normal appearing parenchyma

a) Multi directional diffusion tensor imaging: characterization of fibers’ properties.

b) Emerging as a “resilience factor” in stroke and older age.

RESEARCH OPPORTUNITIES:
- Spatio-temporal patterns of change indicate window of opportunity in early/late middle age.
- Influence of risk factors
- Interactions w/ demographics, multi-morbidities

NAWM (FA)
Example 4: WMH.

a) Volumetric, semi-automated methods

b) Many risk factors well known, in large, longitudinal studies

c) As early as middle-age.

d) Complex interactions w/ age, race, sex, APOe4

e) RCT targeting RF for WMH : modest/no results

RESEARCH OPPORTUNITIES:
- interactions w/ demographics, length of exposure, other morbidities.

Knowledge gaps to understand plasticity

- Better understand age-related CNS characteristics and underlying mechanisms.

- Moderating effects of these CNS changes on plasticity: threshold effects?

- Moderating effects of demographics, length of exposure to risk factors, multi-morbidities.

Research Opportunities.

- Multi-modal and repeated CNS assessments in vivo w/ ex-vivo validations.

- Careful sample selection to leverage the heterogeneity of aging processes to explain inter-subject variability:
  - wide range of age (e.g. prior to middle-age) and of health-related factors;
  - information on time of exposure to risk factors;

http://www.humanconnectomoproject.org/
https://abcdstudy.org/
Conclusions:

- Age-related CNS change can drive functional decline either directly or by weakening the potential for plasticity.

- Whether intervening on age-related CNS change can also promote plasticity needs to be studied.

- Studies should integrate cutting edge CNS assessments w/ traditional methods, both in vivo and ex-vivo, and maintain a focus on state of the art study designs and careful population selection.
THANK YOU

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