No Brain is an Island
Considerations in the ICU

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Objectives of this Talk:
Considerations for research into ICU and Cognition

1. Choose projects that are important and about which you are passionate.
2. Make it as simple as possible, but not simpler.
3. Focus on potentially modifiable targets.
4. Consider where your work fits on the translational continuum.
5. Pick projects in areas where you have local expertise.
6. Try to construct a narrative arc.
1. An Important Public Health Challenge

Up to 9 out of 10 intensive care unit (ICU) survivors will suffer some degree of cognitive impairment at hospital discharge and approximately half will have decrements that persist for years.
Which domains are impaired?

ICU-related neurocognitive impairments occurred in many cognitive domains and are particularly pronounced with regard to memory, executive functions, attentional functions, and processing speed.
Relationship to neuropsych disorders

• Depression
• PTSD
• Pain
• Anxiety
• Mental health related QOL
2. “Make things as simple as possible, but not simpler.”
This is probably not a simple model.
Damage to or dysfunction of which organs carries a cognitive cost?

True, but too simple
Factors conspiring to damage the brain

**Predisposing Factors**
- Advanced age
- Multiple medical comorbidities
- Pre-existing cognitive impairments

**Factors Associated with Critical Illness**
- Hypoxemia
- Hypotension
- Sepsis
- Blood glucose dysregulation

**Other ICU Factors**
- Medications
- Mechanical ventilation
- Inflammatory mediators
- Metabolic disturbances
- Neurotransmitter imbalances
- Cholinergic deficiency

Experimental studies have served to explore the possible mechanisms or pathways involved in this lung to brain interaction.
Mechanism

This communication can be mediated via a complex web of signaling events involving neural, inflammatory, immunologic and neuroendocrine pathways.

Prevention

MV can affect respiratory networks and the application of protective ventilation strategies is mandatory in order to prevent adverse effects. Therefore, strategies focused to minimize lung stretch may improve outcomes, avoiding failure of distal organ, including the brain.
4. Translational Continuum

- **T0**: Basic and Preclinical Research
- **T1**: Translation to Humans
- **T2**: Translation to Patients
- **T3**: Clinical Implementation
- **T4**: Healthcare Delivery and Policy

Cognitive Consequences of Critical Illness and Critical Care
5. Local Expertise

- Delirium
- Sleep medicine
- Genomics
- Dementia
- Imaging
- Neurophysiology
- Specific organ systems (e.g., heart, liver, kidney)
- Specific diseases (e.g. sepsis, ARDS)
- Microbiome
First Steps

Identifying objective risk factors and risk markers are first steps towards developing and effectively targeting interventions to prevent post-ICU cognitive impairment.
Sleep and circadian dysfunction

Potential neurobiological mechanisms including accumulation of beta amyloid pathology, abnormalities of tau, synaptic abnormalities, changes in hippocampal long-term potentiation, impaired hippocampal neurogenesis and gene expression changes.

A study demonstrating the prevalence of sleep abnormalities after critical illness and their longitudinal association with cognitive impairment would yield potential targets for therapy and novel endpoints for ICU-based studies.

Neurophysiology

Although it is an imperfect tool, EEG may be able to provide prognostic information. If quantitative EEG is linked with long-term cognitive outcomes, it may serve as a good intermediate endpoint in therapeutic trials assessing interventions to decrease the risk of post-ICU cognitive impairment.
Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour

The gut microbiota

The human gastrointestinal tract is inhabited by $1 \times 10^{13}$ to $1 \times 10^{14}$ microorganisms — more than 10 times that of the number of human cells in our bodies and containing 150 times as many genes as our genome — and the gut microbiota is therefore often referred to as the forgotten organ.
Neural, Endocrine and Immune Pathways

Healthy status
• Normal behaviour, cognition, emotion, nociception
• Healthy levels of inflammatory cells and/or mediators
• Normal gut microbiota

Stress/disease
• Alterations in behaviour, cognition, emotion, nociception
• Altered levels of inflammatory cells and/or mediators
• Intestinal dysbiosis

6. The PICS Narrative
**Bundle to Prevent PICS**

**Assess, prevent & manage pain**
- CPOT or BPS to assess pain, insure adequate pain control
- Use of regional anesthesia and nonopioid adjuncts
- Analgesia-based sedation techniques with fentanyl

**Both SAT & SBT**
- Daily linked SAT and SBT
- Multidisciplinary coordination of care
- Faster liberation from MV

**Choice of sedation**
- Targeted light sedation when sedation necessary
- Avoidance of benzodiazepines
- Dexmedetomidine if high delirium risk, cardiac surgery, MV weaning

**Delirium monitoring & management**
- Routine CAM-ICU or ICDSC assessments
- Nonpharmacologic intervention, including sleep hygiene
- Dexmedetomidine or antipsychotic if hyperactive symptoms

**Early mobility & exercise**
- Physical and occupational therapy assessment
- Coordinate activity with SAT or periods of no sedation
- Progress through range of motion, sitting, standing, walking, ADLs

**Family engagement & empowerment**
- Reorientation, provision of emotional and verbal support
- Cognitive stimulation, participation in mobilization
- Participation in multidisciplinary rounds
Mitigation

Long-term neurocognitive impairments experienced by critically ill survivors may be mitigated by early interventions, combining cognitive and physical therapies.
Psychological and neurocognitive management options available for critically ill patients

<table>
<thead>
<tr>
<th>Preventative strategies</th>
<th>Neurorehabilitative strategies</th>
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</thead>
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<tr>
<td>Adherence to PAD guidelines</td>
<td>Patient diaries</td>
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<tr>
<td>Use of the ‘ABCDE’ bundle</td>
<td>Follow-up clinics</td>
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<tr>
<td>Music therapy</td>
<td>Follow-up visit</td>
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<tr>
<td>Early psychological intervention</td>
<td>Focus/Support groups</td>
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<td></td>
<td>Cognitive rehabilitation in combination with physical rehabilitation</td>
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PAD: Pain, Agitation and Delirium; ABCDE: awakening and breathing, choice of sedation with fewer adverse effects, daily delirium monitoring and early mobility exercise.
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No Brain is an Island

No brain is an island entire of itself;
every brain is a piece of the corpus, a part of the human;
if a clot be washed away to the lungs, your grip is the less, as well as if a
prominent artery were clogged, as well as any manner of thy
peripherals or of thine vitals were;
any organ's distress diminishes me, because I am involved from heart
to mind.
And therefore never send to know for whom the bell tolls; it tolls for
thee.

With apologies to John Donne