Cognitive and Neuroprotective Effects of Creatine, Citicoline, and Omega 3-Fatty Acids

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Disclosures: Receive industry sponsored research grants and serve as a scientific and legal consultant.
Overview

• Cognitive and Neurological Health Challenges

• Nutritional Interventions
  ▪ Creatine Monohydrate
  ▪ Citicoline
  ▪ Omega 3-Fatty Acids

• Future Research and Opportunities
Cognitive Impairment Challenge

- Cognitive function often declines with age leading to MCI and/or dementia
- Significant interest in finding ways to maintain cognitive function:
  - **Cognitive Activity** (e.g., reading, math, games, puzzles, memory challenges, etc.)
  - **Reduce Stress**
  - **Smoking Cessation**
  - **Weight Management**
  - **Regular Exercise** (enlargement of hippocampus [memory], frontal lobes [executive function], coordination (PCG and cerebellum))
  - **Healthy Diet** (high in berries [polyphenols], leafy greens, vegetables, nuts, beans, whole grains, fish, poultry, olive oil and wine [in moderation])
  - **Nutritional Interventions**
Neuroprotective Challenge

• TBI is an alteration in brain function caused by external trauma that causes temporary and/or permanent cognitive and neurological deficiencies
• Accidents, falls, and combat-related closed brain injury as a result of primary blast injury are common causes of TBI.
• TBI severity ranges from mild with temporary impairment to severe long-term neurological impairment, post-TBI headaches, brain damage, and/or death.
Concussion Challenge

- Sports-related concussions (SRC) or mild TBI are generally more related to blunt force trauma as a result of blows to the head that cause short-term impairment and incrementally greater damage with reoccurrence.
- Individuals who experience a SRC are more susceptible for subsequent and more serious concussions that can often end an athletic career.
- Exposure to repetitive head trauma over time has been associated with Chronic Traumatic Encephalopathy (CTE), neurodegenerative disease, and suicide.
Nutritional Interventions

- Creatine
- Citicoline
- Omega 3-Fatty Acids
CREATINE
Metabolic Role of Creatine


Diagram of metabolic pathways involving creatine and other metabolites.
Ergogenic Value

- Increased single and repetitive sprint performance
- Increased work performed during sets of maximal effort muscle contractions
- Increased muscle mass & strength adaptations during training
- Enhanced glycogen synthesis
- Increased anaerobic threshold
- Possible enhancement of aerobic capacity via greater shuttling of ATP from mitochondria
- Increased work capacity
- Enhanced recovery
- Greater training tolerance
## Creatine & Cognitive Function

<table>
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<tr>
<th>Reference</th>
<th>Population Studied</th>
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<th>Dosage</th>
<th>Findings</th>
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<tr>
<td>McMorris et al. (2006)</td>
<td>20 Health men and women</td>
<td>DBPCPG</td>
<td>19 g/d CrM, 7-d</td>
<td>↓ in performance with sleep deprivation was attenuated with CrM for random movement generation, choice reaction time, balance and mood.</td>
</tr>
<tr>
<td>McMorris et al. (2007)</td>
<td>20 Healthy young sleep deprived men and women</td>
<td>DBPCPG</td>
<td>20 g/d CrM, 7-d</td>
<td>Performance on the random number generation test was improved with CrM</td>
</tr>
<tr>
<td>McMorris et al. (2007)</td>
<td>32 Healthy elderly men and women</td>
<td>DBPCPG</td>
<td>21 g/d CrM, 7-d</td>
<td>Number recall, spatial recall, and long-term memory (photo recall) ↑ with CrM</td>
</tr>
<tr>
<td>Rawson (2008)</td>
<td>21 young health men and women</td>
<td>DBRPCPG</td>
<td>0.03 g/kg/d CrM, 6-wks</td>
<td>NS effects on cognitive performance</td>
</tr>
<tr>
<td>Ling et al. (2009)</td>
<td>47 Healthy young men and women</td>
<td>DBPCPG</td>
<td>5 g/d Cr ethyl ester, 15-d</td>
<td>Some ↑ in all cognitive tests with CrE</td>
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<tr>
<td>Hammett et al. (2010)</td>
<td>Healthy young adults</td>
<td>PCPG</td>
<td>20 g/d CrM 5-d, 5 g/d 2-d</td>
<td>↑ backward digit span performance (26.9%), NS ↑ in RAPM (9.6%), fMRI amplitude ↓ (16%) with Cr</td>
</tr>
<tr>
<td>Benton and Donohoe (2011)</td>
<td>182 healthy females students (Vegan, Meat Eaters, Control)</td>
<td>DBRPCPG</td>
<td>20 g/d, 5-d CrM</td>
<td>Word recall ↓ ME, ↑ Vegan with Cr, Cr better maintained pre- post performance</td>
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<tr>
<td>Cook et al. (2011)</td>
<td>Sleep deprived Rugby Players</td>
<td>BRCRM</td>
<td>50 or 100 mg/kg BW CrM, 1-d</td>
<td>Cr reversed sleep deprived reduction in passing accuracy. &gt; 100 mg/kg</td>
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<tr>
<td>Alves et al. (2013)</td>
<td>45 healthy older women</td>
<td>DBRPCPG</td>
<td>20 g/d 5-d CrM, 5 g/d 24 wks</td>
<td>NS - cognitive performance</td>
</tr>
<tr>
<td>Rae and Broer (2015)</td>
<td>45 healthy young vegan men and women</td>
<td>DBRPCCO</td>
<td>5 g/d CrM, 6-wks</td>
<td>CrM ↑ performance on the RAPM test under time pressure, and digit span task.</td>
</tr>
<tr>
<td>Turner et al. (2015)</td>
<td>15 Healthy male and females exposed to hypoxia</td>
<td>DBRPCCO</td>
<td>20 g/d CrM, 7-d, 5-wk washout between trials</td>
<td>Brain [Cr] ↑. CrM offset hypoxia-induced ↓ in cognitive tests, particularly complex attention.</td>
</tr>
<tr>
<td>Merege-Filho et al. (2017)</td>
<td>72 Healthy male and female children (10-12 yrs)</td>
<td>DBRPCPG</td>
<td>0.3 g/kg/d, 7-d</td>
<td>Cognitive function and brain creatine levels were not influenced by CrM</td>
</tr>
</tbody>
</table>

*Dolan, Gualano, Rawson. Eur J Sport Sci. Epub: August 9, 2018*
Potential for use of creatine supplementation following mild traumatic brain injury

Dean et al. Concussion. CNC34, 2017

Figure 1. The neurometabolic cascade after mTBI, and its overlap with creatine biology (in red). (A) How diffuse injury after mTBI results in large-scale membrane depolarisation (a ‘spreading depression’-like state), reduced blood flow and increased intracellular calcium. (B) The generalised cellular energy crisis, where large amounts of ATP are required to repolarise the membranes and counteract the ‘spreading depression’-like state. This occurs in a low oxygen environment, with dysfunctional mitochondria (due to calcium sequestering), resulting in increased glycolysis and lactic acid formation, along with increased oxidative stress and potential formation of mPTP. (C) The secondary effects of increased intracellular calcium. Red boxes and arrows indicate the role and influence of creatine within mTBI neuropathology.

https://www.futuremedicine.com/doi/pdf/10.2217/cnc-2016-0016
Beyond muscle: the effects of creatine supplementation on brain creatine, cognitive processing, and traumatic Brain Injury
Dolan, Gualano, Rawson. Eur J Sport Sci. Epub: August 9, 2018

Panel A: Acute stressors (e.g. sleep deprivation, exhaustive exercise, acute hypoxia, cognitively demanding tasks or mTBI) can cause a reduction in brain creatine, thus impacting brain function. Preventive supplementation creates a ‘reserve’ of brain creatine, protecting against the reduction caused by anticipated acute stressors, facilitating maintenance of usual brain function.

Panel B: Some conditions are associated with chronically reduced brain creatine, e.g. cerebral creatine deficiency syndromes, depression, schizophrenia or senescence. Therapeutic creatine supplementation restores brain creatine content, facilitating recovery of usual brain function.
Dietary supplement creatine protects against traumatic brain injury


- Adult ICR mice (40) and adult Sprague-Dawley rats (24) underwent controlled cortical contusions that mimick human closed-head injury.
- Animals received daily injections of CM or olive oil for 1, 3, and 5-days before injury.
- CM ameliorated the extent of cortical damage by as much as 36% in mice and 50% in rats.
- Protection seems to be related to creatine-induced maintenance of mitochondrial bioenergetics.
- Mitochondrial membrane potential was significantly increased, intra-mitochondrial levels of reactive oxygen species and calcium were significantly decreased, and adenosine triphosphate levels were maintained.
- Induction of mitochondrial permeability transition was significantly inhibited in animals fed creatine.
- Creatine may provide clues to the mechanisms responsible for neuronal loss after traumatic brain injury and may be useful as a neuroprotective agent against acute and delayed neurodegenerative processes.
Six-day-old rats received subcutaneous CrM injections for 3-d (3 g/kg body weight/day), followed by MRS.

In a second group, rats received the same Cr dose as above for 3 days prior to unilateral common carotid artery ligation followed by 100 min of hypoxia (8% O2).

Cr supplementation for 3 days significantly increased brain energy potential (i.e., the ratio of PCr/betaNTP and PCr/Pi) as measured by 31P-MRS.

Rats with cerebral hypoxic-ischemic insult that received Cr showed a significant reduction (25%) of the volume of edemic brain tissue vs. controls.

Prophylactic Cr supplementation demonstrated a significant neuroprotective effect 24 h after transient cerebral HI.
**Prophylactic creatine administration mediates neuroprotection in cerebral ischemia in mice.** Zhu et al. *J Neurosci.* 24(26):5909-12, 2004

- Evaluated the effect of creatine supplementation on an *experimental stroke model*.
- **Oral creatine** administration resulted in a *remarkable reduction in ischemic brain infarction and neuroprotection after cerebral ischemia in mice*.
- Postischemic caspase-3 activation and cytochrome c release were significantly reduced in creatine-treated mice.
- Creatine buffered ischemia-mediated cerebral ATP depletion.
- **Creatine might be considered as a novel therapeutic agent for inhibition of ischemic brain injury in humans.**

- Male mice were fed a diet supplemented with 0%, 1%, 2% or 5% creatine for 3-wks.
- **Middle cerebral artery occlusion (MCAO)** was performed to elicit an experimental stroke. Cerebral blood flow and the size and volume of the infarct was quantified after 4-d.
- Creatine supplementation produced minor and non-significant changes in brain creatine, phosphocreatine, adenosine triphosphate, adenosine diphosphate and adenosine monophosphate levels.
- **Mice fed creatine had better cerebral blood flow (CBF) after stroke and improved vasodilatory responses** in isolated middle cerebral arteries.
- There was a **40% reduction in infarct volume** after transient focal cerebral ischemia.
- Our data suggest that **creatine-mediated neuroprotection can occur independent of changes in the bioenergetic status of brain tissue, but may involve improved cerebrovascular function.**
Creatine monohydrate supplementation for 10 weeks mediates neuroprotection and improves learning/memory following neonatal hypoxia ischemia encephalopathy in female albino mice. *Allah et al. Brain Res. 21;1595:92-100, 2015*

- Mice were subjected to left carotid artery ligation followed by 8% hypoxia for 25 minutes.
- After 10-d, mice were divided into Normal rodent diet, 1% and 3% creatine supplemented diets for 10 weeks.
- A battery of neurological tests (Rota rod, open field and Morris water maze) to assess neurofunction.
- Cr significantly improved locomotory and exploratory behavior
- Cr showed better neuromuscular coordination (rota rod) and improved spatial memory (Morris Water Maze test).
- Cr significantly reduced reduced infarct volume size.
- Mice supplemented with 3% Cr for 10 weeks performed better during Morris water maze test while 1% Cr supplementation improved the exploratory behavior and gain in body weight than control group.
- Cr supplementation has the potential to improve the neurofunction following neonatal brain damage.
20 adult rats were fed for 4 weeks with or without creatine (5 g CM / 100 g dry food) before undergoing a moderate spinal cord contusion.

Following an initial complete hindlimb paralysis, rats of both groups substantially recovered within 1 week.

CM fed animals scored 2.8 points better than the controls in the BBB open field locomotor score (11.9 and 9.1 points respectively after 1 week; P=0.035, and 13 points compared to 11.4 after 2 weeks).

All animals developed a cavity around the injury.

Cr feeding resulted in a significantly smaller amount of scar tissue surrounding the cavity.

Creatine feeding reduced the spread of secondary injury.

Our results favor a pretreatment of patients with creatine for neuroprotection in cases of elective intramedullary spinal surgery.
Creatine diet supplement for spinal cord injury: influences on functional recovery and tissue sparing in rats  

- Spinal cord injury (SCI) instruments (NYU and Infinite Horizon [IH] methods) were used to assess the efficacy of creatine-supplemented diets on hind limb functional recovery and tissue sparing in adult rats.
- Rats were fed control versus 2% creatine-supplemented chow for 4-5 weeks prior to SCI (pre-fed), after rats resumed a control or 2% control diet (pre & post-fed).
- Following long-term behavioral analysis (BBB), the amount of spared spinal cord tissue among the dietary regimen groups was assessed using stereology.
- Relative to the control fed groups injured with either method, none of the creatine fed animals showed improvements in hind limb function or white matter tissue sparing.
- Although creatine did not attenuate gray matter loss in the NYU cohort, it significantly spared gray matter in the IH cohort with pre-fed and pre & post-fed regimens.
- Such selective sparing of injured spinal cord gray matter with a dietary supplement yields a promising strategy to promote neuroprotection after SCI.

- 14 individuals with were randomized to creatine (3g daily), vitamin D (25000 IU each two weeks) or placebo group in a double-blind design.
- All participants performed progressive resistance training during eight weeks.
- 71.4% of participants had deficit values of vitamin D.
- The corrected arm muscle area improved significantly (p<0.05) in creatine group relatively to the control group.
- There was a significant correlation (p<0.05) between the one repetition maximum Pec deck and levels of vitamin D.
- Supplementation with creatine may improve muscle strength parameters in individuals with spinal cord injury.
- Vitamin D deficiency is highly prevalent in this population.
- It is recommended an initial screening of vitamin D levels at the beginning of the physical rehabilitation process.
“These findings provide strong evidence that creatine supplementation may limit damage from concussions, TBI, and/or SCI.”

“...government legislatures and sport organizations who restrict and/or discourage use of creatine may be placing athletes at greater risk—particularly in contact sports that have risk of head trauma and/or neurological injury thereby opening themselves up to legal liability.”

https://jissn.biomedcentral.com/articles/10.1186/s12970-017-0173-z
CITICOLINE
Metabolic Role of Citocoline

https://www.neuraxpharm.it/en/vivifast-more-info-a/
Neuroprotection afforded by prior citicoline administration in experimental brain ischemia: effects on glutamate transport


- Focal brain ischemia was produced in Fischer rats by occluding both the common carotid and middle cerebral arteries.
- Citicoline (0.5, 1 and 2 g/kg i.p. administered 1 h before the occlusion) produced a reduction of the infarct size measured at striatum by 18%, 27% and 42% inhibition, respectively, compared to 5% in control ischemia.
- Response correlated with an increase in glutamate.
- Citicoline also inhibited ischemia-induced decrease in cortical and striatal ATP levels.
- Incubation of cultured rat cortical neurones with citicoline (10 and 100 microM) prevented OGD-induced LDH and glutamate release and caused a recovery in ATP levels after OGD.
- Citicoline increased glutamate uptake and in EAAT2 glutamate transporter membrane expression in cultured astrocytes.
- Results show novel mechanisms for the neuroprotective effects of citicoline, which cooperate to decrease brain glutamate release after ischemia.
Citicoline enhances frontal lobe bioenergetics as measured by phosphorus magnetic resonance spectroscopy


- Phosphorus (³¹P) metabolite data were acquired using a 3D chemical-shift imaging protocol at 4 T from 16 healthy men and women who orally self-administered 500 mg or 2,000 mg Cognizin Citicoline for 6 weeks.
- Significant increases in phosphocreatine (+7%), beta-nucleoside triphosphates (largely ATP in brain, +14%) and the ratio of phosphocreatine to inorganic phosphate (+32%), as well as significant changes in membrane phospholipids, were observed in the anterior cingulate cortex after 6 weeks of citicoline treatment.
- Citicoline improves frontal lobe bioenergetics and alters phospholipid membrane turnover.
- Citicoline supplementation may therefore help to mitigate cognitive declines associated with aging by increasing energy reserves and utilization, as well as increasing the amount of essential phospholipid membrane components needed to synthesize and maintain cell membranes.
The effect of citicoline supplementation on motor speed and attention in adolescent males


- 75 healthy adolescent males were randomly assigned to either the citicoline group (n = 51 with 250 or 500 mg citicoline) or placebo (n = 24).
- Participants completed the Ruff 2&7 Selective Attention Test, Finger Tap Test, and the Computerized Performance Test, Second Edition (CPT-II) at baseline and after 28 days of supplementation.
- Citicoline improved attention (p=0.02) and increased psychomotor speed (p=0.03) compared to placebo.
- Higher weight-adjusted dose significantly predicted increased accuracy on an attention task (p = 0.01), improved signal detectability on a computerized attention task (p = 0.03), and decreased impulsivity (p = 0.01).

- 60 healthy adult women were assigned to: PLA, 250 mg citicoline, or 500 mg citicoline for 28 –d.
- Participants were evaluated with the Continuous Performance Test II (CPT-II), a measure sensitive to attentional function.
- After 28-d of supplementation, individuals in the 250 mg group made fewer omission (p = 0.04) and commission (p = 0.03) errors vs. PLA.
- Individuals in the 500 mg group made significantly fewer commission errors compared to those in the PLA and trended toward making fewer omission errors (p = 0.07).
- Citicoline may improve attentional performance in middle-aged women and may ameliorate attentional deficits associated with central nervous system disorders.

Table 2. 250 mg compared to placebo: CPT-II omission and commission errors at time 3.

<table>
<thead>
<tr>
<th></th>
<th>250 mg (N = 20)</th>
<th>Placebo (N = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time 3 CPT-II Omission Errors Mean ± SE</td>
<td>0.90 ± 0.25</td>
<td>6.70 ± 3.11</td>
</tr>
<tr>
<td>Time 3 CPT-II Commission Errors Mean ± SE</td>
<td>2.70 ± 0.77</td>
<td>5.50 ± 1.03</td>
</tr>
</tbody>
</table>

Table 3. 500 mg compared to placebo: CPT-II omission and commission errors at time 3.

<table>
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<th></th>
<th>500 mg (N = 19)</th>
<th>Placebo (N = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time 3 CPT-II Omission Errors Mean ± SE</td>
<td>1.47 ± 0.66</td>
<td>6.70 ± 3.11</td>
</tr>
<tr>
<td>Time 3 CPT-II Commission Errors Mean ± SE</td>
<td>2.68 ± 0.75</td>
<td>5.50 ± 1.03</td>
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</table>
In a multi-site study, 265 patients (>65 yrs) with memory complaints but no deficit were supplemented with 500 mg of citicoline twice daily for 9 months (1 g/d) and compared to 84 controls treated with usual care. Mini-Mental State Examination (MMSE) scores remained unchanged over time with citicoline whereas scores declined in PLAN with treatment values significantly higher than controls at 3 & 9 mo.

• No differences were found in Activities of Daily Living (IADL) scales.
• A statistical trend was found in Geriatric Depression Scale (GDS) score (p = 0.06).
• Citicoline was effective and well tolerated in patients with mild vascular cognitive impairment.
Multicenter observational program for evaluation of the effectiveness of the recognan (citicoline) in the correction of cognitive impairment in patients with chronic cerebrovascular pathology  


- **736 patients** with cerebrovascular pathology, cognitive impairment and mild dementia
- 279 (37.9%) men and 457 (62.1%) women aged from 35 to 80 years (mean age 64.5+/−8.7 years).
- Recognan (citicoline) was administered in the dose of **1,000 mg/d for 30 days**.
- Citicoline improved cognitive function, memory and visual/spatial coordination and a decreased depression severity.
- **Citicoline reduced cognitive dysfunction and disturbances of visual/spatial coordination as well as had a positive effect on the emotional sphere decreasing the level of depression.**
Docosahexaenoic acid (DHA) (22:6n–3)  
Eicosapentaenoic acid (EPA) (20:5n–3)
Role of Omega-3 FA in Mild TBI

- Mitigate pathophysiological events after injury.
- Increase the expression of protective mediators.
- Improve functional outcomes after injury.

The protective effect of fish n-3 fatty acids on cerebral ischemia in rat prefrontal cortex Ozen et al. Neurol Sci. 29(3):147-52, 2008

- Cerebral ischemia and reperfusion was produced in rats fed Control, Standard diet, or Standard diet plus fish n-3 EFA for 14 days.
- Malondialdehyde (MDA) levels, activities of superoxide dismutase (SOD), catalase (CAT), and number of apoptotic neurons was determined.
- The levels of MDA and activities of SOD increased in rats on a standard diet compared to control and decreased in rats fed n-3 EFA compared to standard diet.
- The activities of CAT increased in rats fed n-3 EFA compared to standard diet.
- The number of apoptotic neurons in prefrontal cortex was lower with n-3 EFA compared to a standard diet.
- Dietary supplementation of fish n-3 EFA may be beneficial to preserve or ameliorate the ischemic cerebral vascular disease.
Fish oil improves motor function, limits blood-brain barrier disruption, and reduces Mmp9 gene expression in a rat model of juvenile traumatic brain injury

*Russell et al. Prostaglandins Leukot Essent Fatty Acids. 90(1):5-11, 2014*

- 17-day old Long-Evans rats were given a **15mL/kg fish oil** (2.01g/kg EPA, 1.34g/kg DHA) or **soybean oil** dose via oral gavage **30min prior** to a **controlled cortical impact injury** or sham surgery, followed by **daily doses for 7-d.**
  - **Fish oil** treatment resulted in **less severe hindlimb deficits after TBI** as assessed with the beam walk test, **decreased cerebral IgG infiltration,** and **decreased TBI-induced expression of the Mmp9 gene 1-d after injury.**
  - Results indicated that **fish oil improved functional outcome after TBI resulting, at least in part from decreased disruption of the blood-brain barrier through a mechanism that includes attenuation of TBI-induced expression of Mmp9.**
Mice were subjected to sham operation or controlled cortical impact, followed by random assignment of (1) control; (2) daily intraperitoneal injections of n-3 PUFAs for 2 weeks, beginning 2 h after TBI; (3) fish oil supplementation throughout the study, beginning 1 day after TBI; or (4) combination of treatments (2) and (3) for 35-d.

Spatial cognitive deficits, chronic brain tissue loss, and endogenous brain repair processes were evaluated for 35 days after TBI. Fish oil and supplementation with n-3 PUFA attenuated cognitive deficits without reducing gross tissue loss.

The combined treatment promoted post-TBI restorative processes in the brain, including generation of immature neurons, microvessels, and oligodendrocytes which correlated with improved cognitive recovery.

Repetitive and prolonged n-3 PUFA treatments after TBI are capable of enhancing brain remodeling and could be developed as a potential therapy to treat TBI victims in the clinic.
Reversing brain damage in former NFL players: Implications for traumatic brain injury and substance abuse rehabilitation


- 30 retired NFL players with brain damage and cognitive impairment participated in this study.
- Participants lost weight (if needed) and ingested 5.6 g/d of fish oil; a multi-vitamin; and, a brain enhancement supplement containing ginkgo, vinpocetine, acetyl-l-carnitine, huperzine A, alpha-lipoic acid and n-acetyl-cysteine for an average of 6-months.
- Outcome measures were Microcog Assessment of Cognitive Functioning and brain SPECT imaging.
- In the retest situation, corrected for practice effect, there were statistically significant increases in scores of attention, memory, reasoning, information processing speed and accuracy on the Microcog cognitive function assessment.
- The brain SPECT scans, as a group, showed increased brain perfusion, especially in the prefrontal cortex, parietal lobes, occipital lobes, anterior cingulate gyrus and cerebellum.
- Cognitive and cerebral blood flow improvements are possible in this group with multiple interventions.
Limited effect of omega-3 fatty acids on the quality of life in survivors of traumatic injury: A randomized, placebo-controlled trial

- This study investigated **the effects of DHA supplementation on QOL in survivors of TBI**.
- In this secondary analysis of a double-blind, randomized controlled trial, 53 participants received DHA-rich supplements and 57 received PLA for 12 weeks.
- The Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) was used to assess QOL.
- **DHA did not significantly affect any QOL** domain on the SF-36 **after 12 weeks**.
- In the DHA group, changes in the erythrocyte levels of EPA as well as DHA + EPA were positively correlated with the SF-36 mental component.
- **DHA did not influence QOL of trauma patients, but increased EPA levels during the trial were associated with better QOL in patients receiving omega-3.**
CREATINE

CITICOLINE

OMEGA-3 FATTY ACIDS
Combination of creatine, an omega-3 fatty acid, and citicoline
PCT/US2015/014856 University of Utah / Perry Renshaw (inventor)

Claims: “Improvement of neuropsychological performance, ...treatment of a depression disorder, ...improvement of complexion in a subject.”
Creatine | Citicoline | Omega-3 Fatty Acids

Cognitive Impairment?
Mild & Traumatic Brain Injury?
Sport Concussion?
Chronic Traumatic Encephalopathy (CTE)?
Spinal Cord Injury?
Depression and/or Suicide Prevention?
Future Research

- Maintaining cognitive function as one ages and finding ways to reducing the incidence and/or severity of concussion, TBI, CTE, and SCI will continue to be a major public health and research focus.
- Identifying natural compounds that can improve brain health provides a unique opportunity for the supplement and functional food sectors.
- Creatine, citicoline, and ω-3 FA show promise but others need study (GAA, Beta Alanine, Lutein, fruit bioactives, etc.).
- Additional research is needed!
Nutrition & Functional Food Opportunities
Cognitive and Neuroprotective Effects of Creatine, Citicoline, and Omega 3-Fatty Acids

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