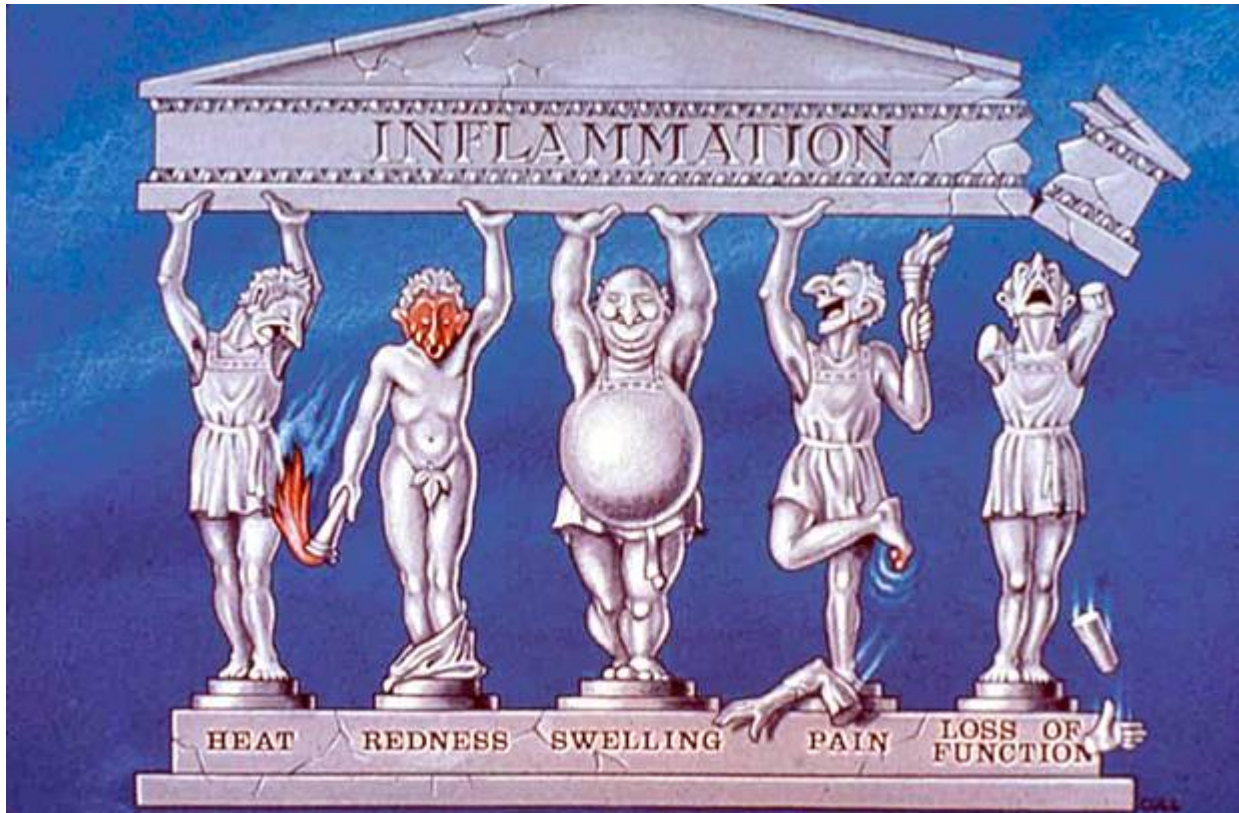


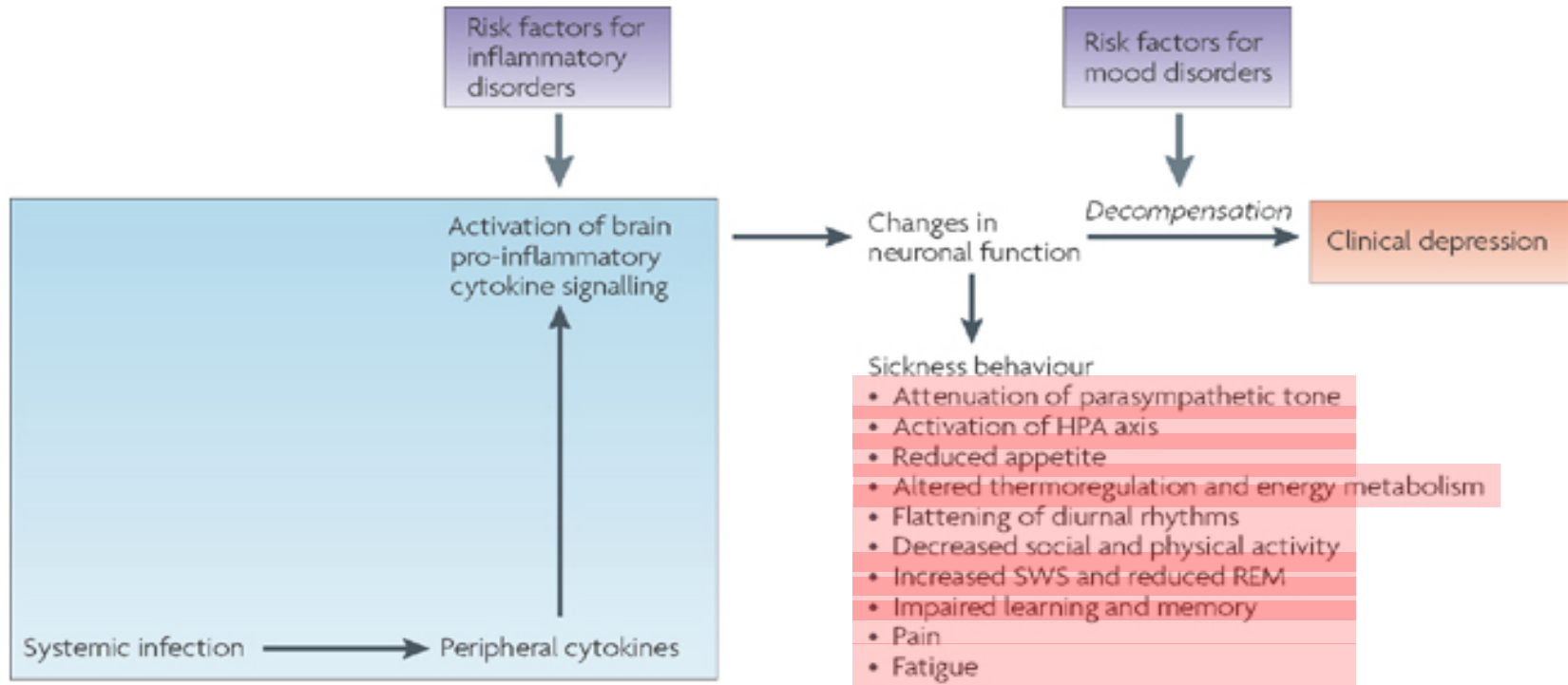
INFLAMMATION AND COGNITION

ONCE UPON A CYTOKINE

FIVE CARDINAL SIGNS OF INFLAMMATION



INFLAMMATION & SICKNESS BEHAVIOUR



SICKNESS BEHAVIOUR

- Decrease in locomotion
- Decrease in social behaviour
- Decrease in sexual behaviour
- Anorexia
- Fever response

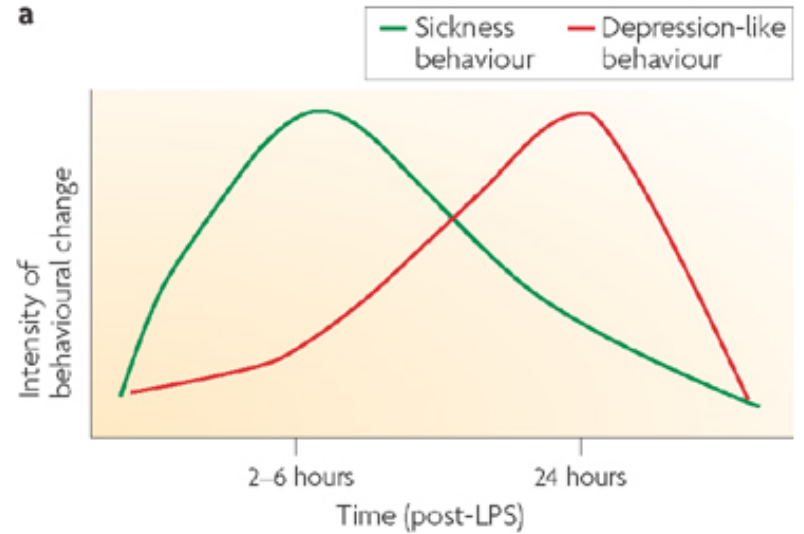
Dantzer 2004

- Cognitive deficits that persist beyond the expression of sickness behaviour

Kohman et al 2007

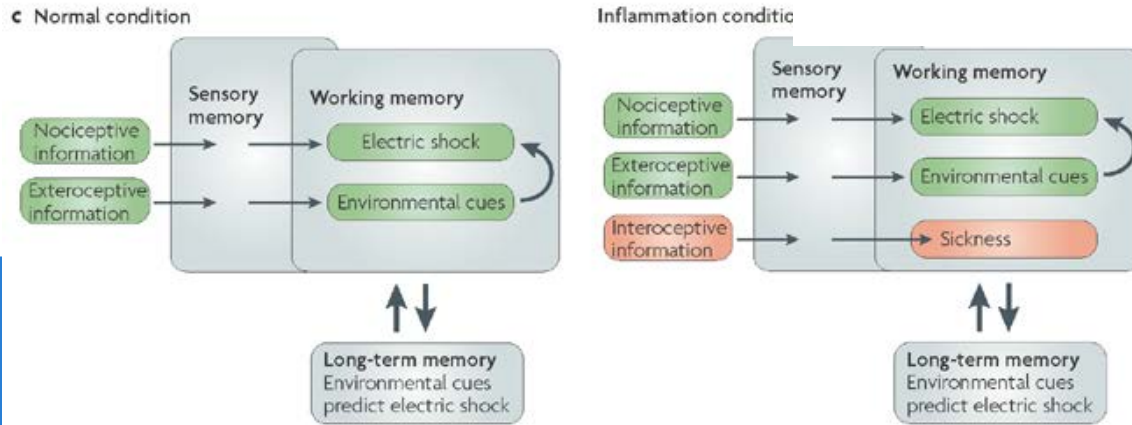
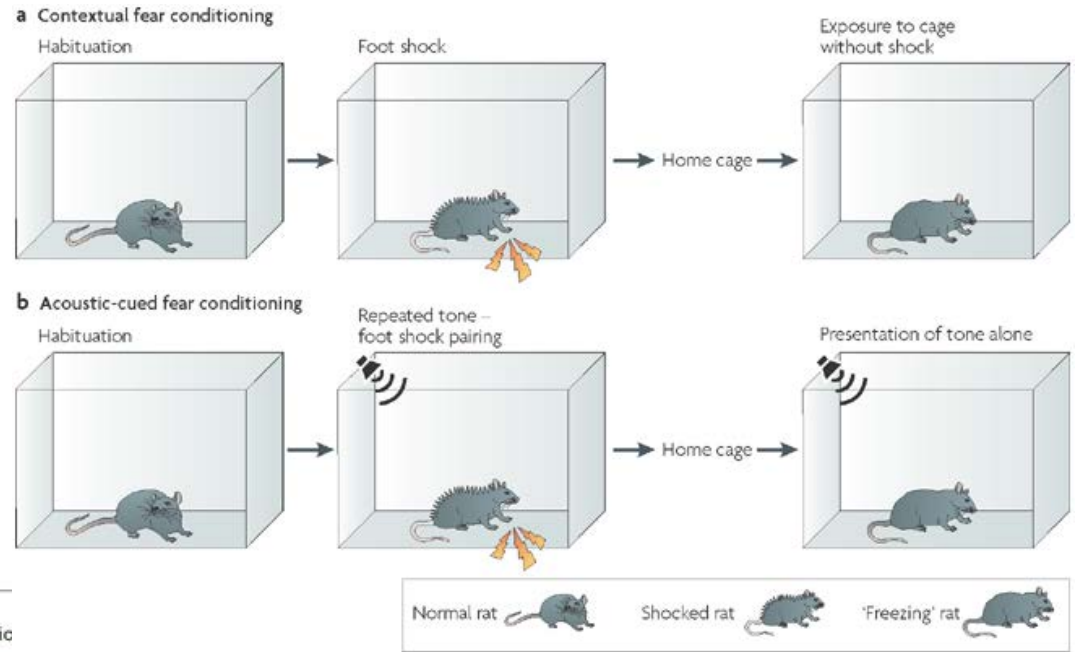


SICKNESS BEHAVIOUR: A MODEL OF DEPRESSION



Nature Reviews | Neuroscience

INFLAMMATION IMPAIRS LEARNING



Nature Reviews | Neuroscience

CYTOKINES ARE INVOLVED IN LEARNING:

IL-1 β , IL-1 α are up-regulated during Long Term Potentiation induction in hippocampus

Schneider et al 1998

Ross et al 2003

IL-1 β injection to brain leads to memory deficits

Matsumoto et al 2004, Moore et al 2009

IL1 receptor implicated in learning

Avital et al 2003, Goshen et al 2007, Spulber et al 2009

Exposure to IL-1Ra in utero leads to cognitive deficits in adulthood

Goshen et al 2007

CYTOKINES ARE INVOLVED IN NEUROGENESIS

PROINFLAMMATORY CYTOKINES IMPAIR

Classically activated microglia which secrete cytokines impair hippocampal neurogenesis

Monje et al 2003, Ekdahl et al 2003

- Diminished cell survival
- Decreased proliferation

Fujioka & Akema 2012

Exposure to IL-1 β , IL-6, and TNF α leads to reduced proliferation

Green et al 2012, Wu et al 2012

Valierres et al 2002

Seguin et al 2009, Hoffer et al 2007

IL-1 β mediates stress induced decrease of neurogenesis

Koo & Duman 2008

ANTI-INFLAMMATORY CYTOKINES PROMOTE

TGF- β

- Increases survival of cells
- Increases hippocampal neurogenesis

Mathieu et al 2010, Battista et al 2006

IL-4 increases microglia expression of IGF-1 and neurogenesis

Annekov 2009

IL-10

- Stimulated microglia enhance NPC in culture
- Secreted by microglia supported neuronal differentiation and new cell survival
- Attenuates the reduction in neurogenesis in Alzheimer mouse model

Kiyota et al 2011, Caccl et al 2008, Kiyota et al 2011

WHAT ABOUT HUMANS?



C-REACTIVE PROTEIN AND GENETIC VARIANTS AND COGNITIVE DECLINE IN OLD AGE

Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial

N=5680 participants

mean age of 75 years

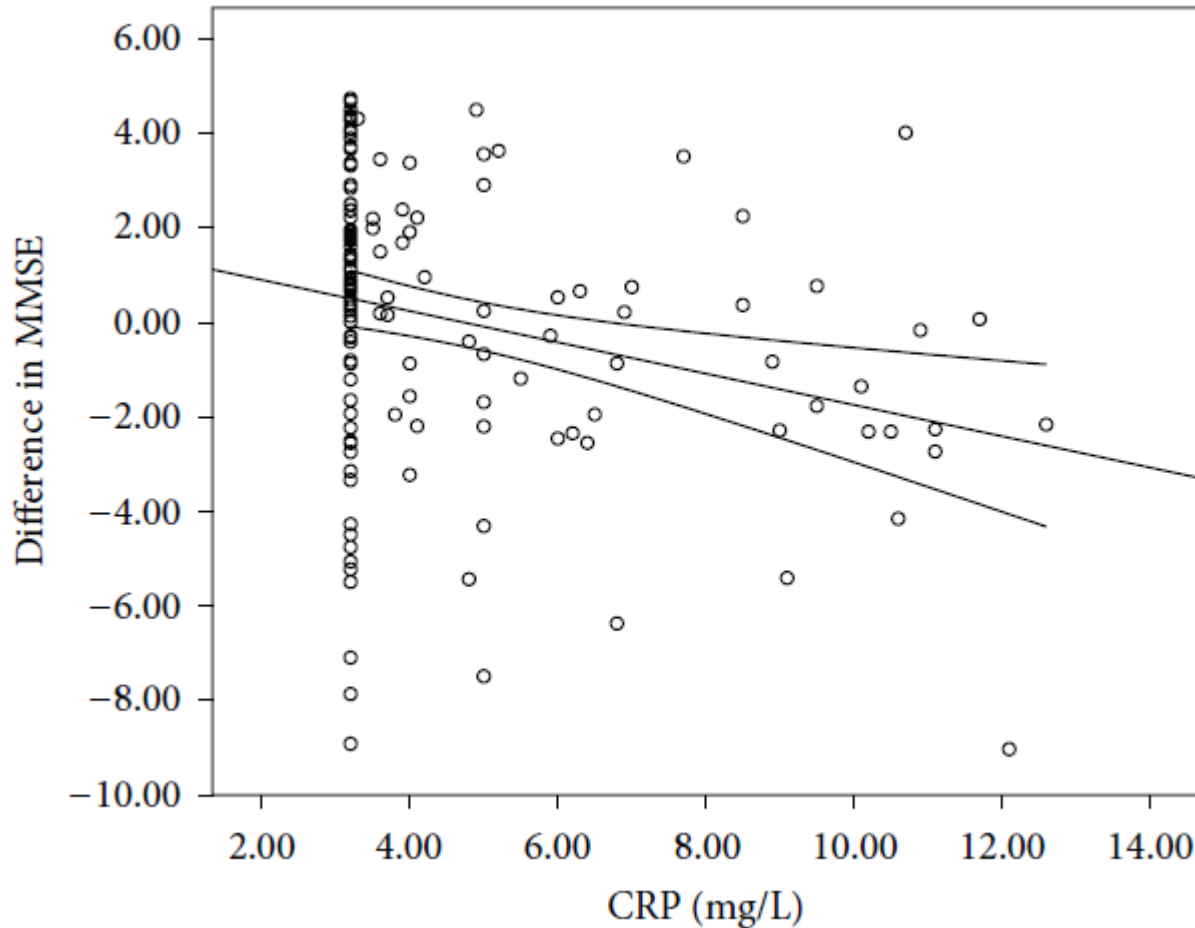
- Higher plasma CRP concentrations were associated
 - poorer baseline performance on the Stroop test ($P=0.001$) and Letter Digit Tests ($P<0.001$)
 - increased rate of decline in the immediate PLT ($P=0.016$)
- In comparison to strong associations of apolipoprotein E with cognitive measures, associations of CRP haplotypes with such measures were inconsistent

C-REACTIVE PROTEIN PREDICTS COGNITIVE DECLINE

- The highest quartile of hs-CRP had significantly more cognitive decline than those in the lowest quartile
- When cases were removed, there was no difference in cognitive decline by CRP quartile
- This relationship was not modified by the presence of apolipoprotein E varepsilon4.
- These findings suggest that inflammatory mechanisms during midlife may reflect underlying processes contributing to dementia-related cognitive decline late in life.

Honolulu-Asia Aging Study (HAAS), a longitudinal community-based study of Japanese American men
hs-CRP levels measured on average 25 years before cognitive testing began in 1991.
Subjects were followed from up to three follow-up examinations (mean of 6.1 years)
Cognitive function was measured with the Cognitive Abilities Screening Instrument (CASI).
This analysis includes a sub-sample of 691 subjects dementia-free in 1991

DECLINE IN MMSE IS ASSOCIATED WITH HIGHER LEVELS OF CRP (P<0.001)



C-REACTIVE PROTEIN AND COGNITION ARE UNRELATED TO LEUKOARAIOSIS

- Patients with CRP levels ≥ 5.0 had 2.9 (95% CI: 1.26-6.44) times more chance to present cognitive impairment (P: 0.012)
- Elevated serum levels of C-reactive protein (CRP) have been associated with leukoariosis in elderly brain
- leukoariosis is associated with an increased risk of cognitive impairment
- coronary patients over 50 years old
- CRP levels explained 7.18% (P: 0.002) of the variance of the MMSE
- The adjustment for the presence of leukoariosis changed this variance only slightly (5.98%, P: 0.005)
 - only a small portion of the CRP influence on cognition was mediated via leukoariosis

C-REACTIVE PROTEIN PLAYS A MARGINAL ROLE IN COGNITIVE DECLINE: A SYSTEMATIC REVIEW AND META-ANALYSIS

- Higher levels of CRP are associated with a significant risk of global cognitive decline (OR, 1.27 [95% CI, 1.02 to 1.58])
- The systematic review from six other articles that were not suitable for meta-analysis revealed a marginal association between CRP and cognitive decline in certain domains

nondementia population

479 related articles from PubMed and Google

4 studies, N=5255 non-demented subjects that report odds ratio (OR)/relative risk/hazard ratio of CRP levels and decline in general cognition met criteria for meta-analysis

HIGHER LEVELS OF CRP ARE CORRELATED TO LOWER COGNITIVE FUNCTION: AGE RANGE 40-54

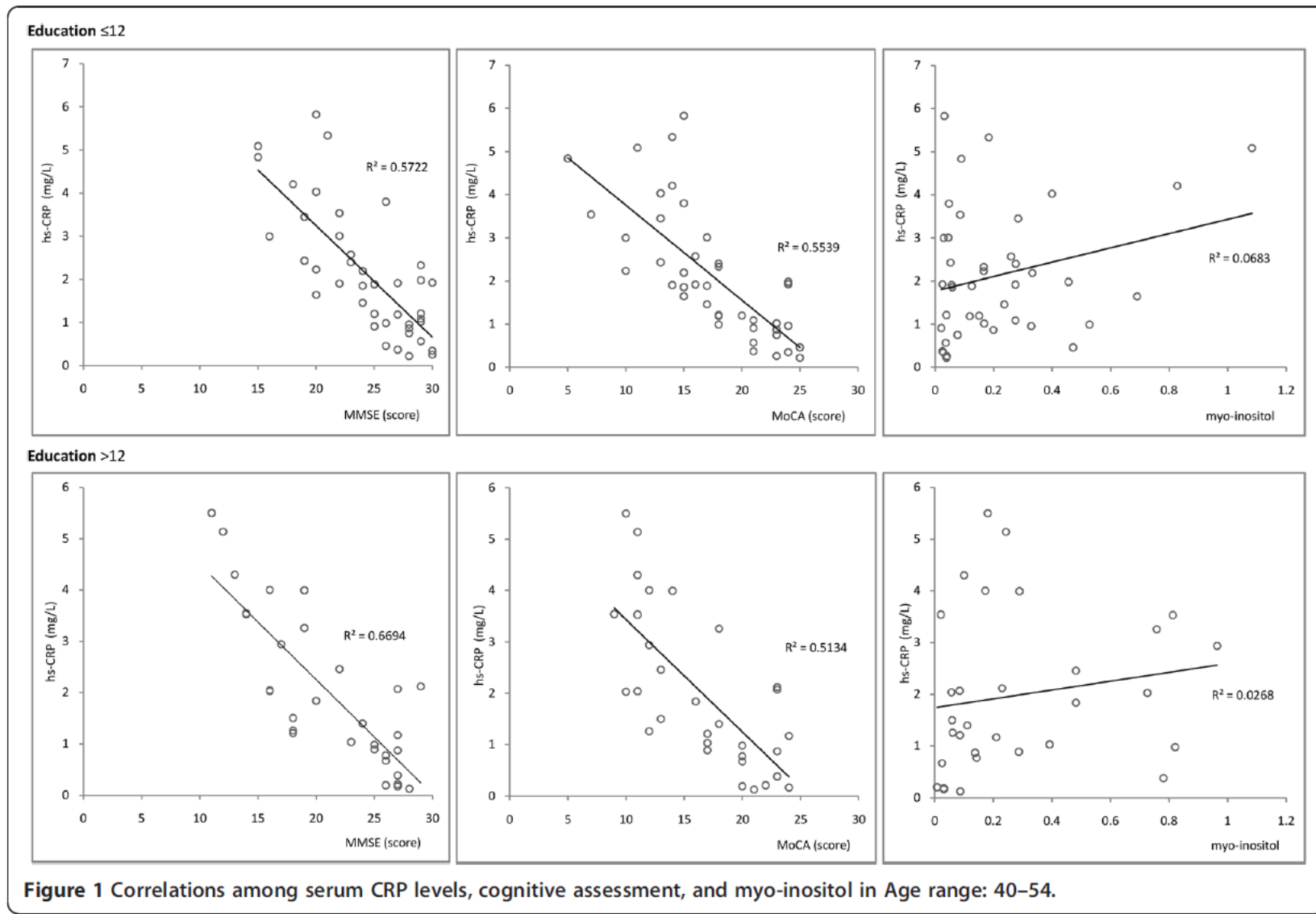


Figure 1 Correlations among serum CRP levels, cognitive assessment, and myo-inositol in Age range: 40–54.

IL-6

INFLAMMATION AND RATE OF COGNITIVE CHANGE IN HIGH-FUNCTIONING OLDER ADULTS

Linear negative relationship between inflammation and cognition:

- higher levels of inflammation are associated with lower levels of baseline cognitive function

After controlling for potential confounders, there was no effect of inflammation on baseline cognitive function or the rate of longitudinal cognitive change

Persons in the top tertile on IL-6 were at an increased risk of incident declines on the Short Portable Mental Status Questionnaire (SPMSQ)

MacArthur Study of Successful Aging
longitudinal cohort study of high-functioning older adults
70-79 years at baseline in 1988
reinterviewed in 1991 and 1995 (N = 851)

INFLAMMATORY MARKERS IN N WELL-FUNCTIONING ELDERS

highest tertile of IL-6 or CRP (compared to lowest tertile)

- performed nearly 2 points lower (worse) on baseline and follow-up 3MS ($p < 0.001$ for all)
- declined by almost 1 point over >2 years ($p = 0.01$ /IL-6 and $p = 0.04$ /CRP)
- more likely to have cognitive decline:
 - IL-6 (26 vs 20%) [OR] = 1.34
 - CRP (24 vs 19%; OR = 1.41)

3MS scores among participants in the highest tertile of IL-6 and CRP were similar at baseline but remained significantly lower at follow-up ($p < \text{or} = 0.05$ for both)

There was no significant interaction between race and inflammatory marker or between nonsteroidal anti-inflammatory drug use and inflammatory marker on cognition

N=3,031 African-American and white men and women (mean age 74 years)
Health, Aging, and Body Composition Study
In age-adjusted analyses

INTERLEUKIN-6 COVARIES INVERSELY WITH COGNITIVE PERFORMANCE AMONG MIDDLE-AGED COMMUNITY VOLUNTEERS

Inverse relationship between circulating levels of IL-6 and performance on clusters of tests assessing auditory recognition memory, attention/working memory, and executive function

No association between IL-6 and performance on tests of general memory.

Secondary analyses demonstrated that relationships between IL-6 and auditory recognition and working memory and executive function were independent of a number of health factors, including body mass index, smoking, and hypertension

500 healthy community volunteers
aged 30 to 54

INTERLEUKIN-6 PREDICTS COGNITIVE DECLINES

- High IL-6
 - reasoning was 0.08 SD (95% confidence interval [CI] -0.14, -0.03) lower than low IL-6
 - 10-year decline in reasoning was greater (ptrend = 0.01) (-0.35; 95% CI -0.37, -0.33) than those with low IL-6 (-0.29; 95% CI -0.31, -0.27)
 - 1.81 times greater odds ratio of decline in MMSE (95% CI 1.20, 2.71)
- CRP was not associated with decline in any test

N=5,217 persons

27.9% women

1991-1993 and 1997-1999

Whitehall II longitudinal cohort study

10-year assessments in 1997-1999, 2002-2004, and 2007-2009

memory, reasoning, and verbal fluency using mixed models.

- Mini-Mental State Examination (MMSE) was administered in 2002-2004 and 2007-2009

Singh-Manoux A et al

INTERLEUKIN-6 PREDICTS COGNITIVE DECLINE

Highest tertile for plasma IL-6:

- Poorer baseline cognitive function (odds ratio [OR])
- At 7 years of follow-up more likely to exhibit declines in cognition (OR = 1.90)
- At 2.5 years IL-6 predicted cognitive decline
 - Second tertile of IL-6 (OR = 2.21)
 - Third tertile (OR = 2.03)

N=779 high-functioning men and women
aged 70 to 79
MacArthur Study of Successful Aging

LONG-TERM SYSTEMIC INFLAMMATION AND COGNITIVE IMPAIRMENT IS FOUND ONLY IN STATIN NONUSERS

■ Statin nonusers:

- High IL-6 at both times → greater risk of cognitive impairment than those with low IL-6 at both times (HR = 3.35, 95% CI = 1.09-10.30)
- Doubling of CRP change over 20 years → cognitive impairment (OR = 1.32, 95% CI = 1.06-1.65)

Doubling of IL-6 change over 20 years → greater odds of cognitive impairment in 2009-2010 in the whole cohort (odds ratio (OR) = 1.40, 95% CI = 1.04-1.89)

Cognitive impairment (Mini-Mental State Examination score <24 or diagnosis of dementia) was ascertained in 1998-2000, 2003-2005, and 2009-2010

INFLAMMATORY MARKERS MAY BE ASSOCIATED WITH SPECIFIC COGNITIVE DEFICITS

- CRP and IL-6 were associated with all cognitive measures in 1997-1999
- After extensive adjustment higher:
 - CRP levels were only associated with poor cognitive performance on the AH4-I (OR=1.38; 95% CI: 1.05-1.82) and Mill Hill (OR=1.52; 95% CI: 1.14-2.03)
 - IL-6 on semantic fluency (OR=1.27; 95% CI: 1.14-2.03)
- Associations were more evident in men than in women
- No clear relationship was observed for decline

The Whitehall II study; ongoing large-scale, prospective occupational cohort study of employees from 20 London-based white-collar Civil Service departments.

3000 males, 1200 female

Inflammatory makers measured in 1991-1993 and five cognitive tests (short-term verbal memory, inductive reasoning (AH4-I), vocabulary (Mill Hill), and phonemic and semantic fluency) performed in 1997-1999 and 2002-2004

CONFOUNDERS

Sex

Age

Muscle quality

Ethnicity?

Statin use

INFLAMMATION AND COGNITIVE FUNCTION IN AFRICAN AMERICANS AND EUROPEAN AMERICANS

- In AAs, higher sTNFR2 was associated with poorer cognition in all domains
 - (global: -0.11, P = .009; processing speed: -0.11, P < .001; language: -0.08, P = .002; memory: -0.09, P = .008; executive function: -0.07, P = .03)
 - sTNFR1 was associated with slower processing speed (-0.08, P < .001) and poorer executive function (-0.08, P = .008)
 - higher CRP was associated with slower processing speed (-0.04, P = .024)
 - higher IL6 was associated with poorer executive function (-0.07, P = .02)
- In EA, only higher sTNFR1 was associated with slower processing speed (-0.05, P = .007)
 - Associations were not found between cognition and sTNFR2, CRP, or IL6 in EA

Cross-sectional analysis

Community cohort study in Jackson, Mississippi, and Rochester, Minnesota.

AAs and EAs : N = 1,965;

age: 26-95

64% women

52% AA

75% with hypertension

SEX DIFFERENCES IN THE ASSOCIATION BETWEEN MUSCLE QUALITY, INFLAMMATORY MARKERS, AND COGNITIVE DECLINE

- Significant positive relationship was found between cognitive functioning and muscle quality for both sex groups
- CRP was found to have a statistically significant negative association with cognitive functioning for females but not males

445 females, 422 males
over age 60

National Health and Nutrition Examination Survey for 2001-2002

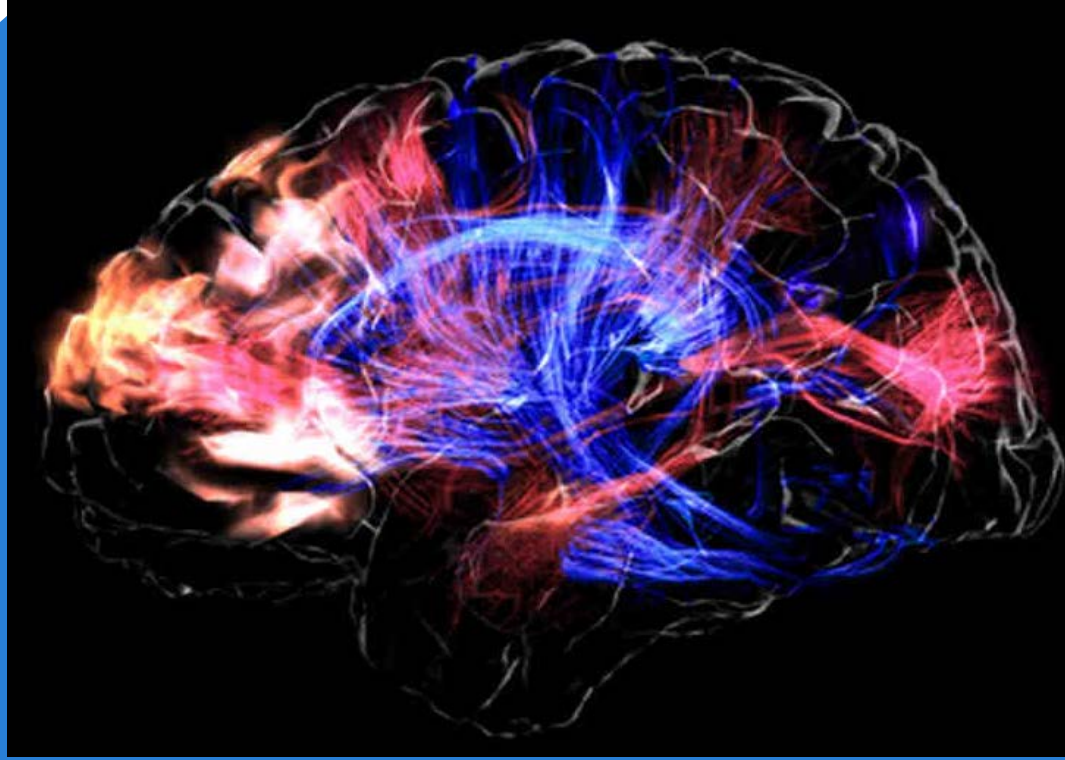
Muscle quality was calculated as isokinetic strength per unit muscle mass.

Participants were assessed for cognitive functioning using the Wechsler Adult Intelligence Scale, Third Edition (WAIS-III) Digit Symbol - Coding module.

High sensitivity C-reactive protein (CRP) assays were performed on blood samples

Canon ME Crimmins EM J Nutr Health Aging. 2011 Aug;15(8):695-8

**MECHANISMS UNDERLYING THE
RELATIONSHIP OF COGNITION AND
INFLAMMATION**



SERUM C-REACTIVE PROTEIN IS LINKED TO CEREBRAL MICROSTRUCTURAL INTEGRITY AND COGNITIVE FUNCTION

Higher levels of hs-CRP were associated with:

- worse performance in executive function after adjustment for age, gender, education, and cardiovascular risk factors in multiple regression analysis (beta = -0.095, p = 0.02)
- reduced global fractional anisotropy (beta = -0.237, p < 0.001)
- regional FA scores :
 - frontal lobes (beta = -0.246, p < 0.001)
 - corona radiata (beta = -0.222, p < 0.001)
 - corpus callosum (beta = -0.141, p = 0.016), in particular the genu (beta = -0.174, p = 0.004)

No association of hs-CRP with measures of white matter hyperintensities or brain atrophy
N=447 community-dwelling and stroke-free individuals from the Systematic Evaluation and Alteration of Risk Factors
for Cognitive Health (SEARCH) Health Study, High-field MRI: 321 of these subjects

248 female
mean age 63 years

INTERLEUKIN-6 COVARIES INVERSELY WITH HIPPOCAMPAL GREY MATTER VOLUME IN MIDDLE-AGED ADULTS

Peripheral levels of IL-6 covaried inversely with hippocampal grey matter volume

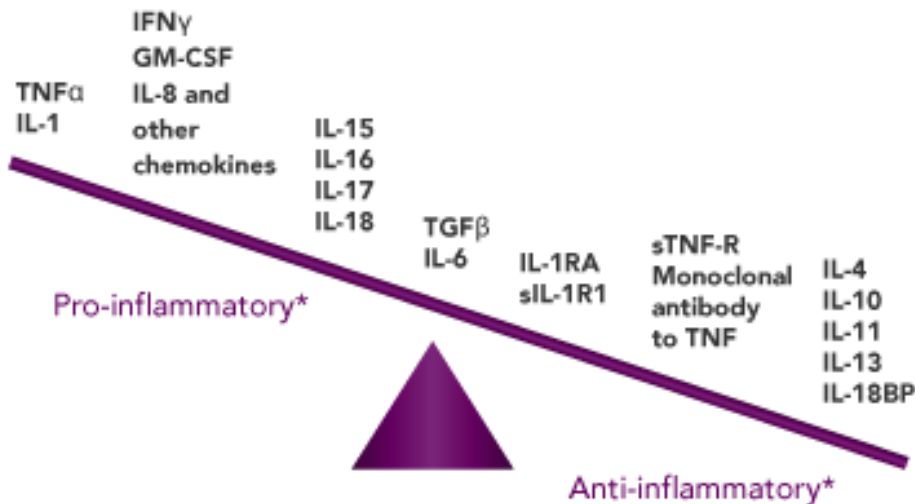
this relationship persisted after accounting for several possible confounders, including age, gender, race, years of education, percent body fat, blood pressure, smoking, physical activity, hours of sleep, alcohol use, and total grey matter volume

76 healthy community volunteers aged 30-54

WHY DO CYTOKINES INCREASE UNDER STRESS?

- Transient activation of the immune system is beneficial
- Induces a neuroinflammatory response which has a detrimental effect on neurogenesis
- Alternatively activated microglia show an increased expression of anti-inflammatory cytokines: IL-10, Transforming growth factor β (TGF- β) Insulin-like growth factor (IGF) , Neural growth factor (NGF), Brain derived neural growth factor (BDNF)
 - Colton 2009
- Anti-inflammatory cytokines IL-4, IL-13 can induce the alternative phenotype

Butovsky et al 2006, Colton 2009



Cytokines drive the inflammatory response⁵

EQUILIBRIUM BETWEEN PRO AND ANTI-INFLAMMATORY EFFECTS OF CYTOKINES

Long term potentiation widely recognized cellular mechanism for learning
and memory

Impaired by inflammation

Cunningham et al 1996, Murray & Lynch 1998

BDNF, NGF, IGF important for memory and learning impaired by
inflammation

Fan et al 1995, Guan & Fang 2006, Kranjac et al 2012, Park et al 2011



SOME CYTOKINES PROMOTE COGNITION

- Exercise-enhances hippocampal neurogenesis
- Environmental enrichment enhances neurogenesis mediated by T-cells

Ziv et al 2006

- IGF-1 increased by voluntary wheel running in adult and aged mice

Kohman et al 2011

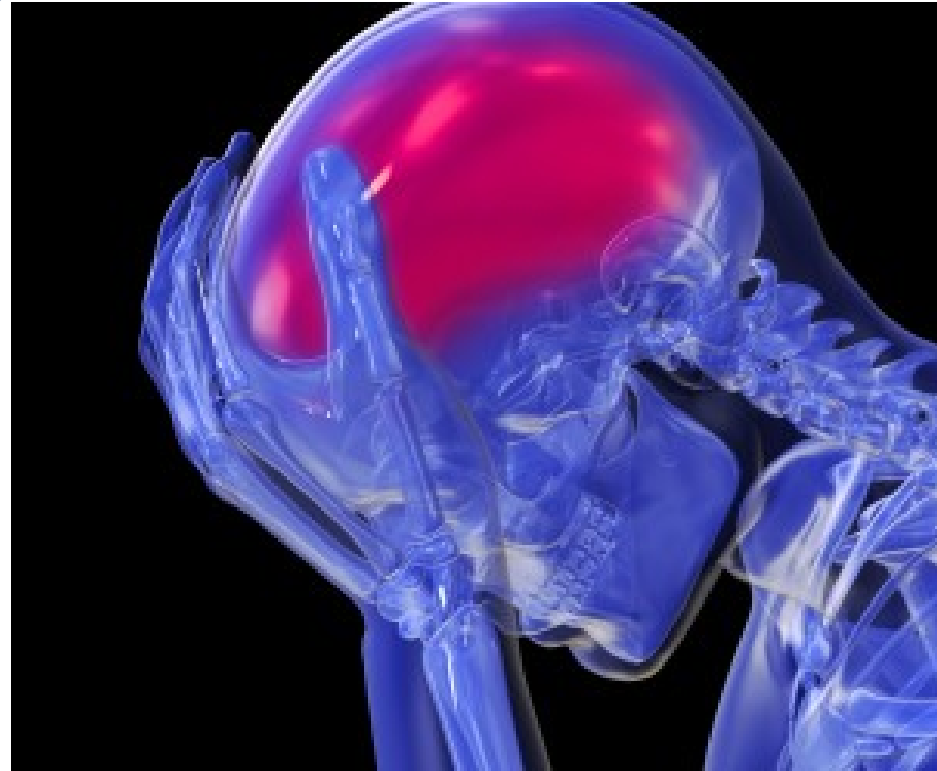
Ziv et al 2006

- Not seen in shorter running periods (10 days versus 8 weeks)

Olah et al 2009



PSYCHIATRIC IMPLICATIONS



**COGNITION, INFLAMMATION AND
SCHIZOPHRENIA**

PERIPHERAL INTERLEUKIN-2 LEVEL IS ASSOCIATED WITH NEGATIVE SYMPTOMS AND COGNITIVE PERFORMANCE IN SCHIZOPHRENIA

Patients with SZ

- lower levels of IL-2 than healthy controls ($p < 0.001$)
- IL-2 levels were positively correlated with scores in the digit span test ($\rho = 0.416$, $P = 0.025$) and intelligence ($\rho = 0.464$, $P = 0.011$)
- a negative correlation between IL-2 and total score in the negative subscale of PANSS ($\rho = -0.447$, $p = 0.015$)

N=29

Chronically medicated outpatients with SZ according to DSM-IV

N=26 healthy controls.

INTERLEUKIN 18 AND COGNITIVE IMPAIRMENT IN FIRST EPISODE AND DRUG NAÏVE SCHIZOPHRENIA VERSUS HEALTHY CONTROLS

77 first episode and drug naïve schizophrenic patients

75 healthy control subjects

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and serum IL-18 in both groups

- For the patients, IL-18 was positively associated with the Visuospatial/Constructional domain of cognitive deficits in schizophrenia
- IL-18 levels were non-significantly higher in patients than controls (206.0 ± 92.9 pg/ml vs 193.2 ± 41.8 pg/ml, $p=0.28$)
- Cognitive scores on the RBANS and nearly all of its five subscales (all $p < 0.05$) except for the Visuospatial/Constructional index ($p > 0.05$) were significantly lower in schizophrenic patients than normal controls

DECREASED INTERLEUKIN-10 SERUM LEVELS IN FIRST-EPIISODE DRUG-NAÏVE SCHIZOPHRENIA: RELATIONSHIP TO PSYCHOPATHOLOGY

- Interleukin-10 (IL-10), a potential anti-inflammatory cytokine is altered in chronic patients with SZ.
- first-episode and drug-naïve (FEDN) patients with SZ = 128
- healthy controls= 62

- patients exhibited a significant decrease in IL-10 levels
- Serum IL-10 was inversely correlated with:
 - PANSS negative symptom subscore in patients
 - PANSS cognitive factor subscore in patients

**COGNITION, INFLAMMATION AND
BIPOLAR DISORDER**

ELEVATED C-REACTIVE PROTEIN IS ASSOCIATED WITH COGNITIVE DEFICITS IN INDIVIDUALS WITH BIPOLAR DISORDER

- Individuals with bipolar disorder show cognitive deficits even in euthymia
- Individuals who had a CRP level higher than the 90th percentile and the 75th percentile () of the control group had significantly increased odds (OR=4.32, $p=.018$, OR=3.07, $p=.04$) of low RBANS total score
- There was an inverse relationship between CRP levels and performance on:
 - RBANS total ($t=-2.48$, $p=.015$)
 - RBANS immediate memory ($t=-2.16$, $p=.033$)
 - RBANS attention ($t=-2.18$, $p=.032$)
 - RBANS language ($t=-2.13$, $p=.036$)
 - Trail Making A ($t=-2.39$, $p=.019$)

N=107

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and the Trail Making Test Part A and WAIS Information and Letter Number Sequencing

the odds of RBANS scores ≤ 70 for participants whose CRP levels were above the 75th and the 90th percentile of the level of non-psychiatric controls

LEVELS OF TNF-A, SOLUBLE TNF RECEPTORS (STNFR1, STNFR2), AND COGNITION IN BIPOLAR DISORDER

N=54 BD type I

N=18 controls

- Higher sTNFR1 and sTNFR2 in BD patients
- No difference was detected between the BD group and the control group for levels of TNF- α

TNF- α level was negatively correlated with the delayed recall in RAVLT

INTERLEUKIN-1 RECEPTOR ANTAGONIST CORRELATES WITH COGNITIVE FUNCTION IN OLDER ADULTS WITH BIPOLAR DISORDER

N=21 BD patients
(65 +/- 9 years)
euthymic

N=26 age-matched
controls

- Interleukin-1 receptor antagonist was elevated in BD subjects compared with controls (439 +/- 326 pg/mL vs. 269 +/- 109 pg/mL; p = 0.004)

- IL-1RA was inversely correlated with three cognitive function factors and global cognition ($r = -0.37$; $p = 0.01$)
- IL-1RA continued to correlate with global cognitive function even when covarying for either IL-6 or brain-derived neurotrophic factor
- FA was lower in BD subjects (0.368 ± 0.02 vs. 0.381 ± 0.01 ; $p = 0.02$)
- IL-1RA was not associated with FA or white matter hyperintensity burden



**COGNITION, INFLAMMATION AND
DEPRESSION**

C-REACTIVE PROTEIN IS NEGATIVELY CORRELATED WITH COGNITIVE PERFORMANCE

- CRP levels increased significantly ($p < 0.001$) over the 6 weeks of treatment
- CRP levels remained significantly high in patients with a higher baseline level ($p < 0.001$)
- baseline CRP level:
 - negatively correlated with performance in the FTT before treatment ($r = -0.580$, $p = 0.006$)
 - significantly correlated with performance in the FTT ($r = -0.501$, $p = 0.021$) and WCST with completed categories ($r = -0.521$, $p = 0.015$) at week 6
- the association between baseline CRP level and HAM-D score was not significant

N=149

MDD

6 weeks of treatment

- total HAM-D scores decreased significantly
- performance in the masked CPT and the WCST with completed categories significantly improved ($p < 0.001$, $p = 0.027$)

IL-6 serum levels is a significant correlate of memory performance

- Encoding and Recall were inversely associated with IL-6 across diagnostic groups after controlling for chronological age, Mini-Mental State Examination, body mass index, literacy level, depression severity, and sex
- Women, in particular, appear sensitive to IL-6 fluctuations across diagnostic groups
- CRP was not associated with cognition
- Depression status was associated with recall independent of IL-6 levels



45 nondepressed

42 depressed

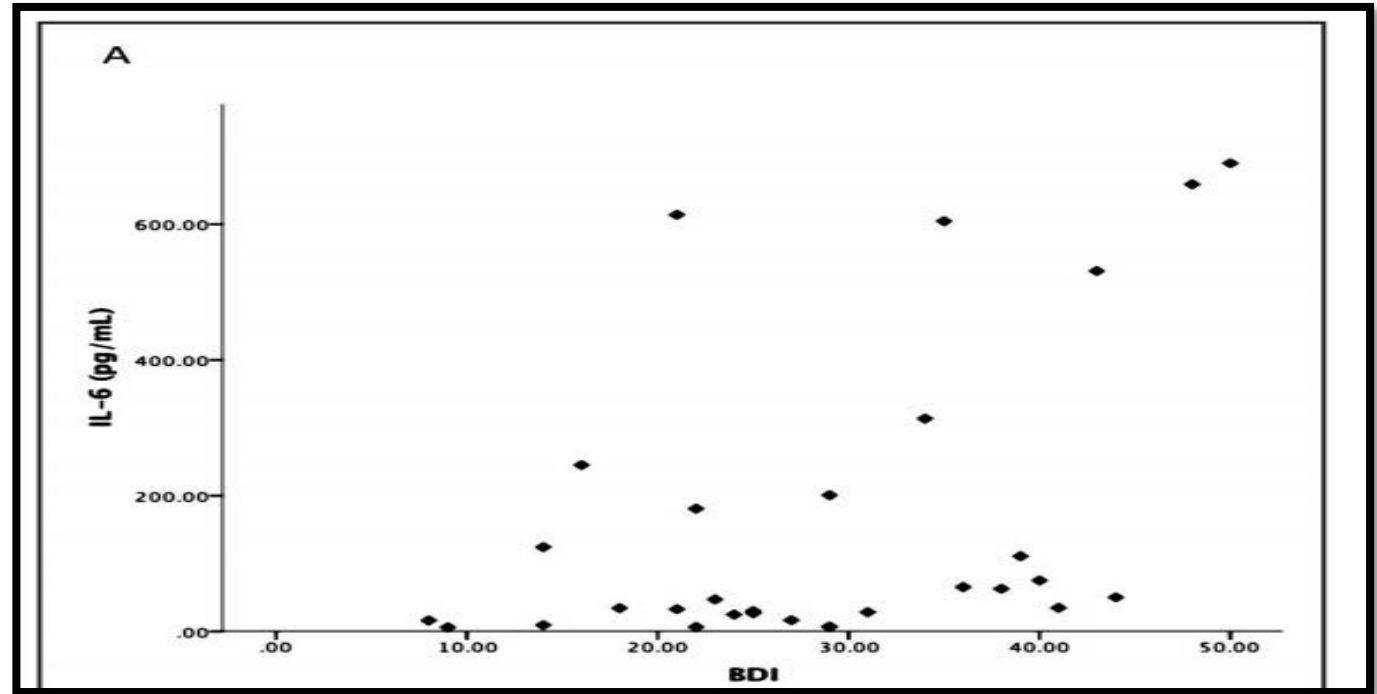
Structured Clinical Diagnostic Interview

neuropsychological examination that assessed memory functions of Encoding and Recall, Executive Function, and Attention/Processing

Mid-morning IL-6 and CRP levels

IL-6 LEVELS IN WOMEN WITH RECURRENT MDD

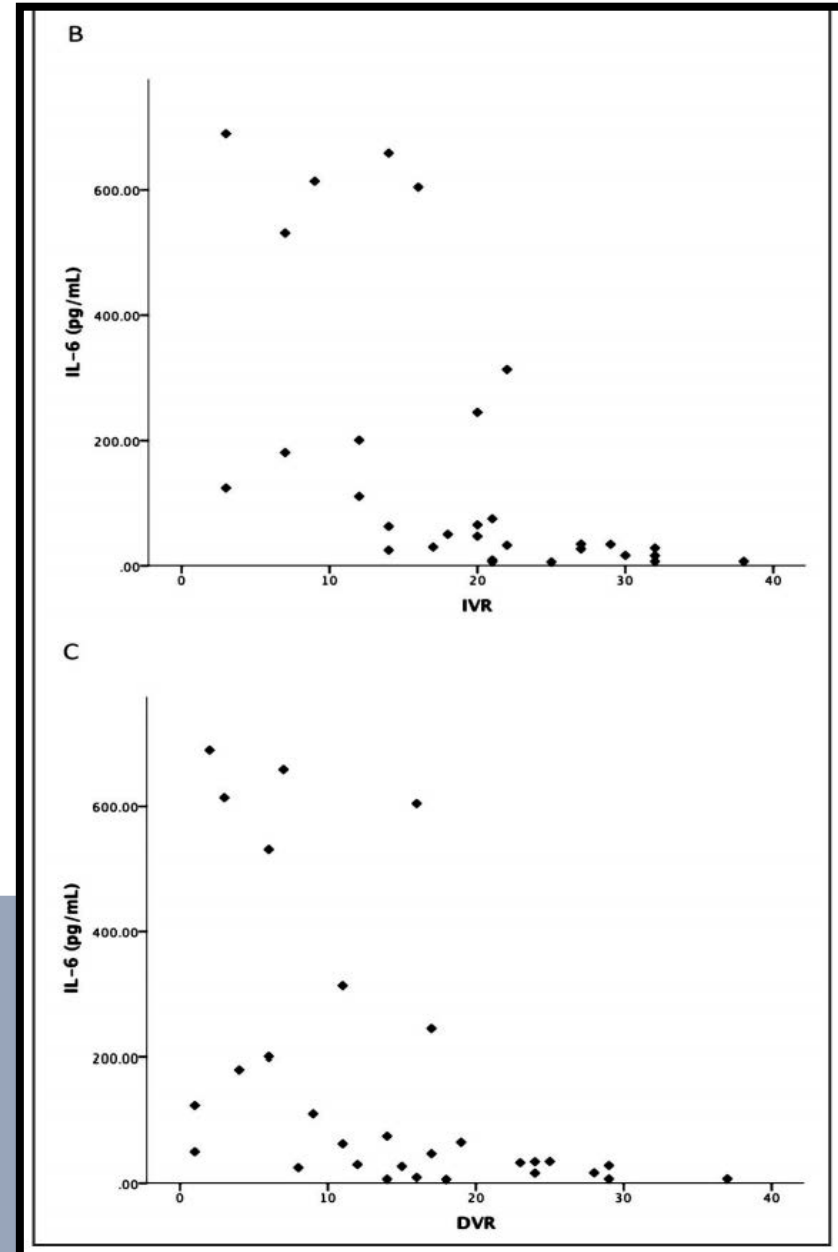
N=30
recurrent major depressive disorder
■ no clinical and psychiatric comorbidities



Beck Depression inventory

LOW PERFORMANCES IN RECALL ARE ASSOCIATED WITH HIGHER IL-6 LEVELS IN WOMEN WITH RECURRENT MDD

- There was a statistically significant association between IL-6 levels:
 - immediate verbal recall (IVR) ($B=-0.787$, $p=0.000$)
 - delayed verbal recall (DVR) ($B=-0.695$, $p=0.001$)
- even after controlling for age, depression severity and body mass index



CONCLUSIONS

- Inflammation is a characteristic of many psychiatric conditions
- Cytokinergic mechanisms may contribute to the cognitive deficits seen in these conditions
- Depression is phenotypically similar to sickness behaviour associated with inflammation and pro-inflammatory cytokines
- Possible pharmacologic and non-pharmacologic interventions may improve cognitive deficits by promoting anti-inflammatory cytokines