NORMENT
Norwegian Centre for
Mental Disorders Research

Immunologiske forhold ved psykoselidelser - muligheter for ny behandling?

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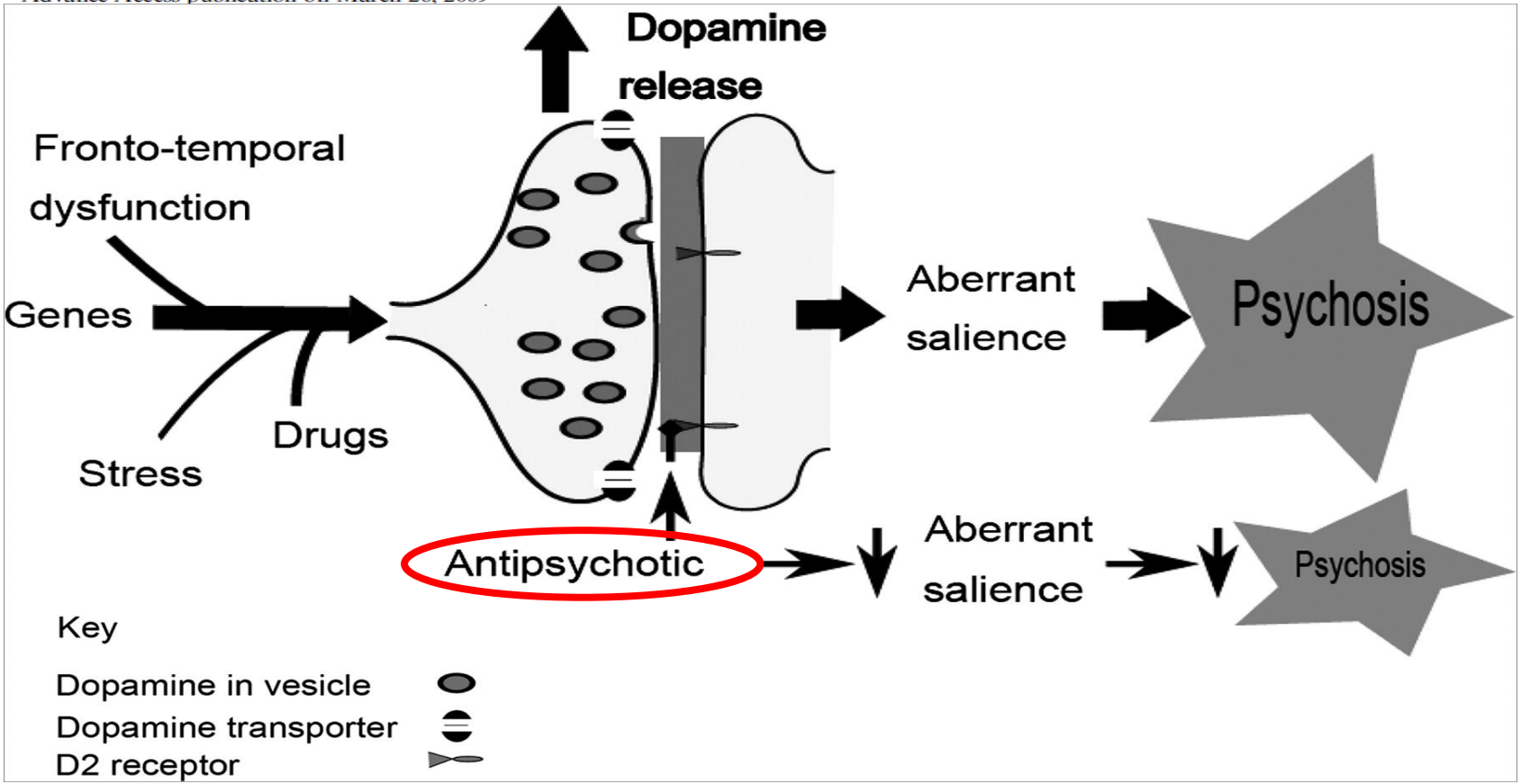
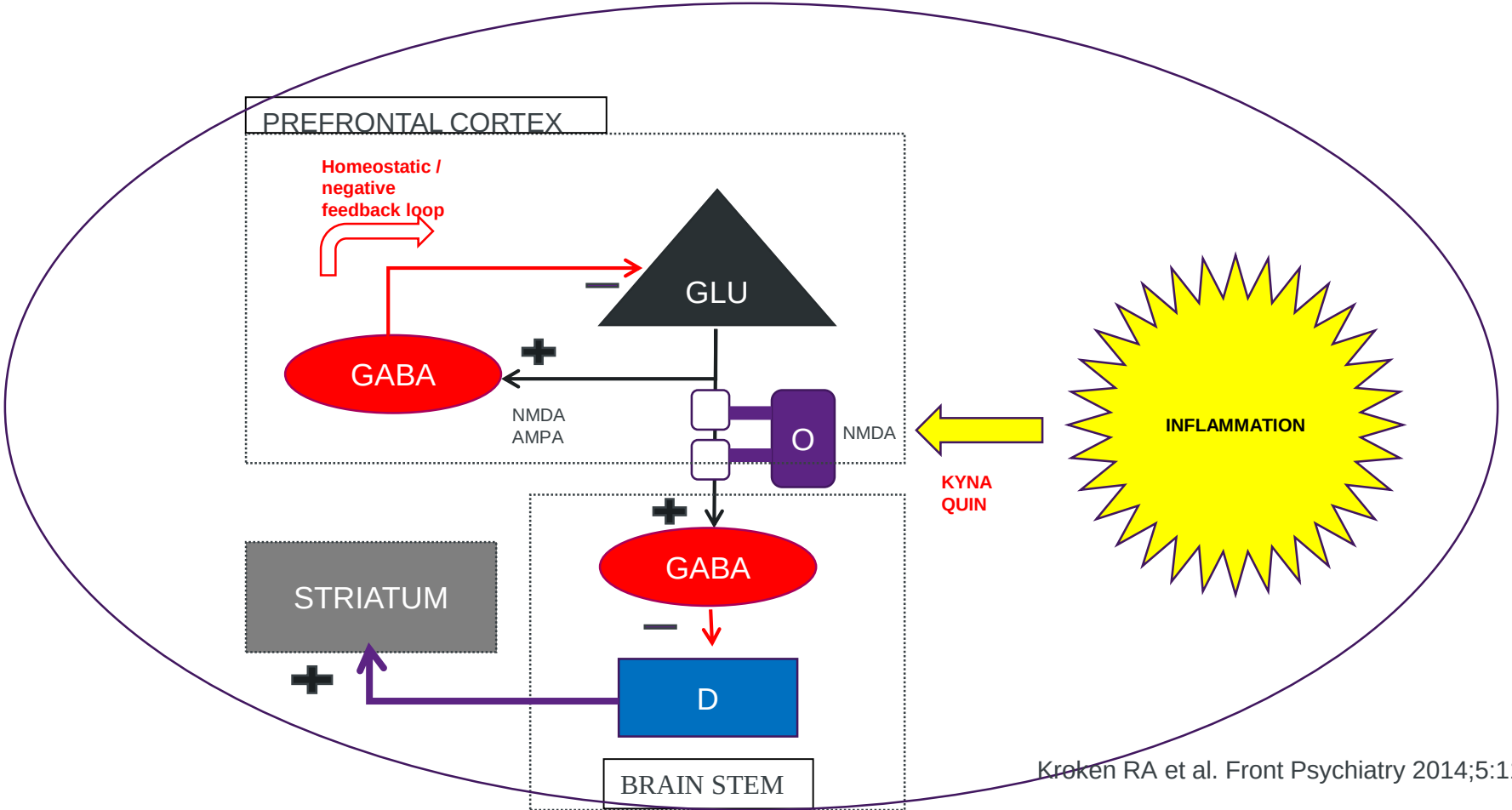
Antipsykotisk effekt vs. symptomområder

- **Positive**
- **Affektive**
- **Negative**
- Kognitive

Schizophrenia Bulletin vol. 35 no. 3 pp. 549–562, 2009
doi:10.1093/schbul/sbp006
Advance Access publication on March 26, 2009





Kroken RA et al. Front Psychiatry 2014;5:11.

Psykose og inflammasjon/ immunologiske prosesser

Historisk kobling mellom immunsystemet og psykose

- 1876—Alexander Rosenblum suggests that typhoid or malaria fever might cure psychosis.
- 1926—Karl Menninger publishes 200 cases of postinfluenzal psychosis; a third of which were reported to resemble dementia praecox (conceptual predecessor of schizophrenia).
- 1927—Julius Wagner-Jauregg is awarded the Nobel prize for medical inoculation of malarial parasites as a treatment for syphilitic psychosis.
- 1929—Moritz Tramer reports an association between schizophrenia and winter or spring birth.
- 1937—Lehman Facius describes autoantibodies against brain structures in the cerebrospinal fluid of patients with schizophrenia.
- 1988—Sarnoff Mednick and colleagues report increased risk of schizophrenia in adult offspring of women pregnant during the 1957 influenza pandemic.
- 1992—Ronald Smith proposes a macrophage-T-lymphocyte theory of schizophrenia.

Khandaker GM et al. Lancet Psychiatry 2015;2:258-70.

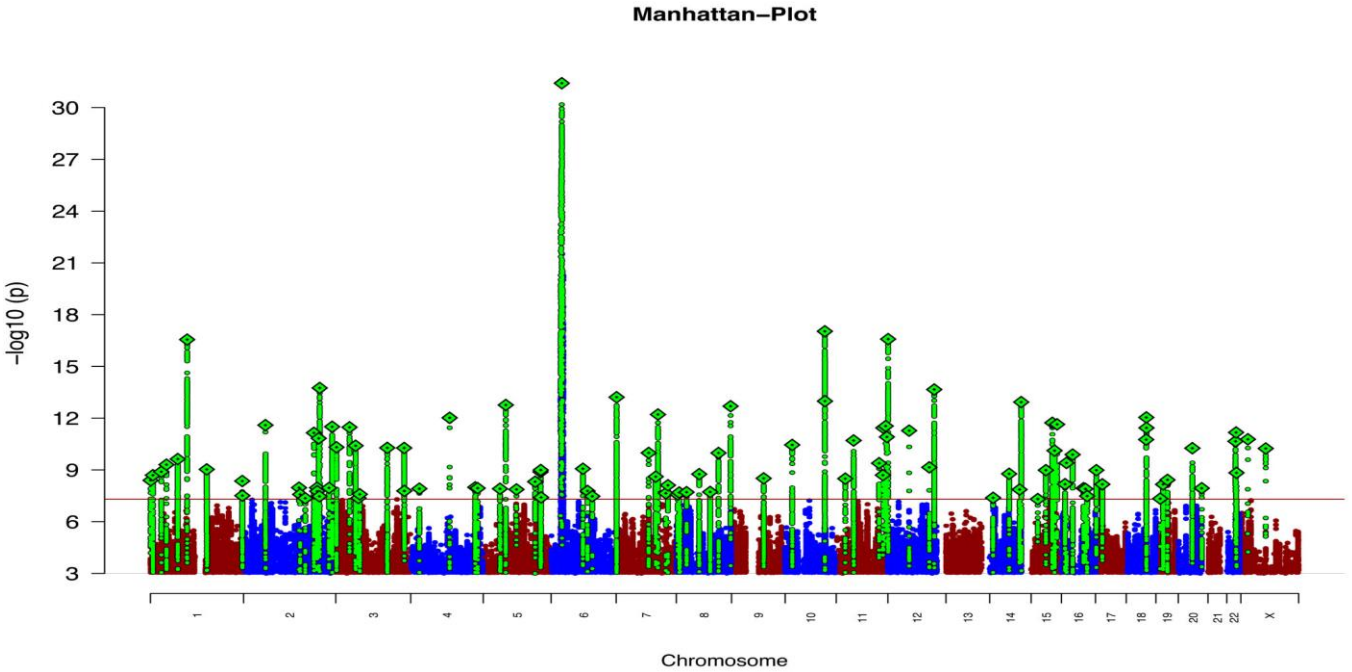
TABLE 2 **Cytokines implicated in the pathogenesis of schizophrenia**

Cytokine (or cytokine receptor antagonist)	Potential source	Role	Dysfunction in schizophrenia
IL-1RA[a]	Lymphocytes	Natural inhibitor of the pro-inflammatory effect of IL-1β Involved in compensatory anti-inflammatory response syndrome (CARS)	Decreased
IL-1β	Macrophages	Pro-inflammatory: activates acute phase proteins	Increased
IL-2	T_h1 lymphocytes	T cell activation: stimulates cell-mediated immunity	Decreased
IL-4	T_h2 lymphocytes	Inhibits IF-γ production: stimulates B cell synthesis of IgE	Increased
IL-6[a]	Monocytes	Pro-inflammatory: induces acute phase proteins	Increased
IL-10	T_h2 and T_{reg} lymphocytes	Anti-inflammatory: inhibits IF-γ production. Involved in CARS	Increased
TNF-α[a]	Macrophages	Pro-inflammatory: induces acute phase proteins	Increased
TGF-β	T lymphocytes	Anti-inflammatory: mucosal immunity and protection. Involved in CARS	Decreased
IF-γ	T_h1 lymphocytes	Macrophage activation	Decreased

a. Most consistent findings. Increase in IL-6 shown to be associated with illness duration and symptom severity.
IF, interferon; IL, interleukin; IL-1RA, interleukin-1 receptor antagonist; TGF, transforming growth factor; TNF, tumour necrosis factor; T_r, regulatory T cell.

Upthegrove,2014

Biological insights from 108 schizophrenia-associated genetic loci



Schizophrenia Working Group of the Psychiatric Genomics Consortium. Nature 2014;511;421-7.

ORIGINAL ARTICLE

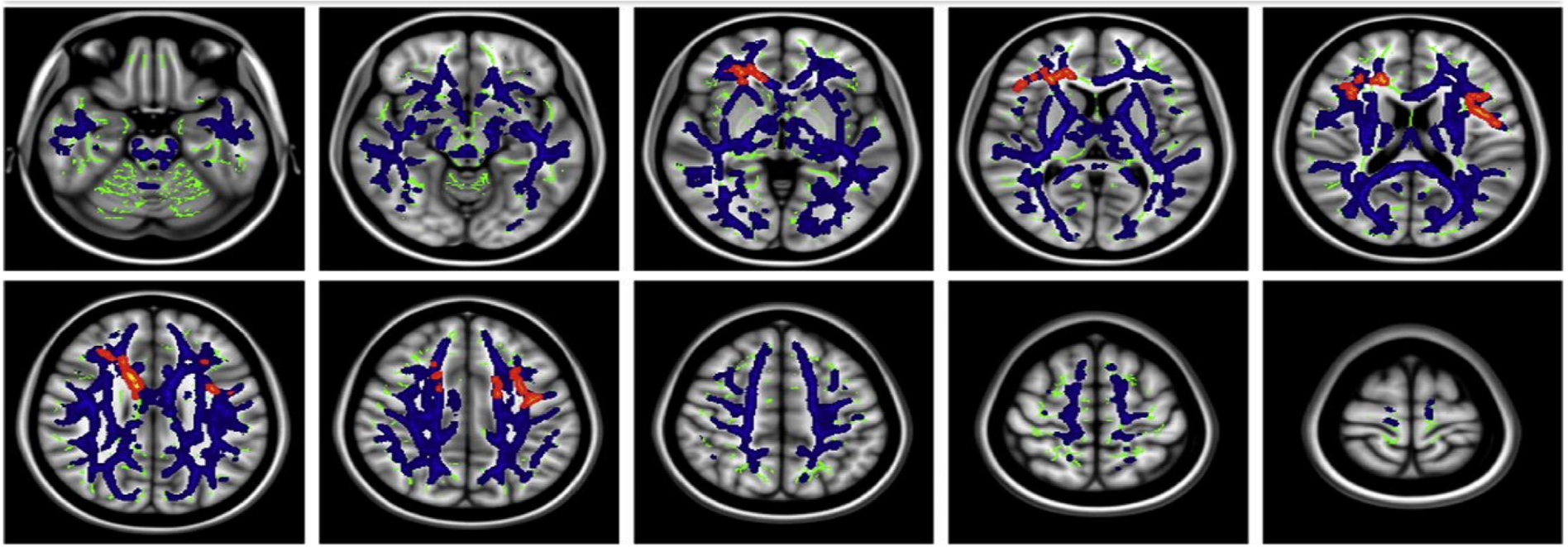
Genetic pleiotropy between multiple sclerosis and schizophrenia but not bipolar disorder: differential involvement of immune-related gene loci

OA Andreassen[1,2,3], HF Harbo[4], Y Wang[1,2,5,6], WK Thompson[3], AJ Schork[5,7,8], M Mattingsdal[1,9], V Zuber[1,2,10], F Bettella[1,2], S Ripke[11,12], JR Kelsoe[3], KS Kendler[13], MC O'Donovan[14], P Sklar[15], The Psychiatric Genomics Consortium (PGC) Bipolar Disorder and Schizophrenia Work Groups[16], The International Multiple Sclerosis Genetics Consortium (IMSGC), LK McEvoy[5,17], RS Desikan[5,17], BA Lie[18], S Djurovic[1,2,18] and AM Dale[3,5,6,17]

Converging evidence implicates immune abnormalities in schizophrenia (SCZ), and recent genome-wide association studies (GWAS) have identified immune-related single-nucleotide polymorphisms (SNPs) associated with SCZ. Using the conditional false discovery rate (FDR) approach, we evaluated pleiotropy in SNPs associated with SCZ ($n = 21\,856$) and multiple sclerosis (MS) ($n = 43\,879$), an inflammatory, demyelinating disease of the central nervous system. Because SCZ and bipolar disorder (BD) show substantial clinical and genetic overlap, we also investigated pleiotropy between BD ($n = 16\,731$) and MS. We found significant genetic overlap between SCZ and MS and identified 21 independent loci associated with SCZ, conditioned on association with MS. This enrichment was driven by the major histocompatibility complex (MHC). Importantly, we detected the involvement of the same human leukocyte antigen (HLA) alleles in both SCZ and MS, but with an opposite directionality of effect of associated HLA alleles (that is, MS risk alleles were associated with decreased SCZ risk). In contrast, we found no genetic overlap between BD and MS. Considered together, our findings demonstrate genetic pleiotropy between SCZ and MS and suggest that the MHC signals may differentiate SCZ from BD susceptibility.

- 33 – 40% ved schizofreni med tegn til lavgradig inflammasjon

Kahn&Sommer. Mol Psychiatry 2015;20:84-97



In conclusion, neuroinflammation is associated with white matter pathology characterized by axonal degeneration, myelin breakdown, reduced density of astroglia and oligodendroglia in selected areas and increased density of white matter neurons among individuals with schizophrenia. Neuroinflammation may contribute to white matter structural and functional disconnectivity, even at the first episode of psychosis

Kognisjon og inflammasjon

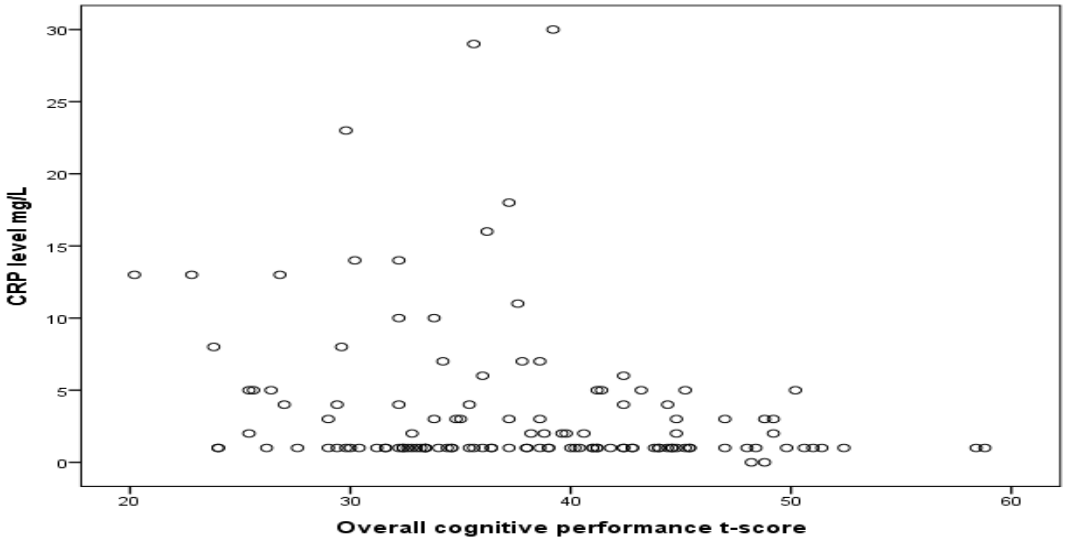
Johnsen et al. BMC Psychiatry (2016) 16:60
DOI 10.1186/s12888-016-0769-x

BMC Psychiatry

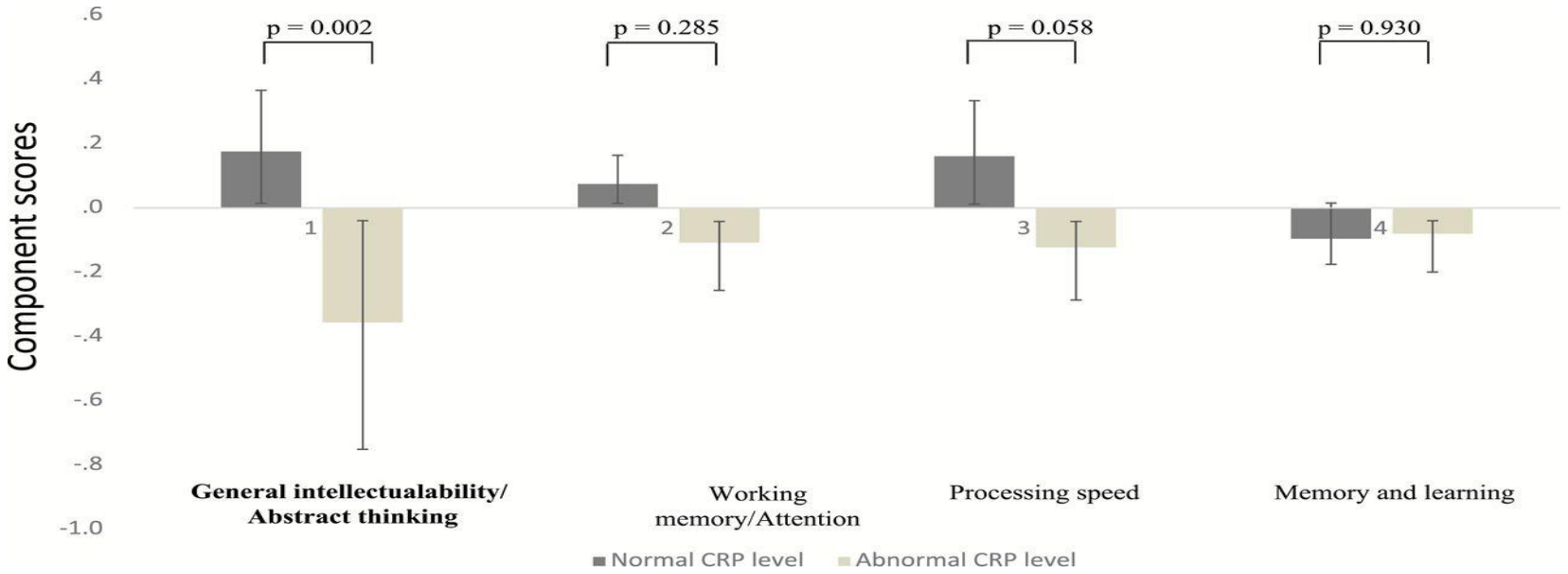
RESEARCH ARTICLE Open Access

The serum level of C-reactive protein (CRP) is associated with cognitive performance in acute phase psychosis

Erik Johnsen[1,2*†], Farivar Fathian[3†], Rune A. Kroken[1,2], Vidar M. Steen[4,5], Hugo A. Jørgensen[2], Rolf Gjestad[1] and Else-Marie Løberg[6,7]



Cognitive impairment associated with chronic peripheral inflammation in schizophrenia (measured by C-Reactive protein [CRP] blood levels ≥3mg/L).



Ewa Bulzacka et al. Schizophr Bull 2016;42:1290-1302

Schizophrenia Research 165 (2015) 188–194

Contents lists available at ScienceDirect

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journal homepage: www.elsevier.com/locate/schres

Inflammatory markers are associated with general cognitive abilities in schizophrenia and bipolar disorder patients and healthy controls

Sigrun Hope [a,b,*], Eva Hoseth [a,d], Ingrid Dieset [a,d], Ragni H. Mørch [a,d], Monica Aas [a,d], Pål Aukrust [c,f,h,i], Srdjan Djurovic [a], Ingrid Melle [a,d], Torill Ueland [a,g], Ingrid Agartz [a,e], Thor Ueland [c,h,i], Lars T. Westlye [a,d,g], Ole A. Andreassen [a,d,h]

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Could antiinflammatory agents have beneficial effects in schizophrenia?

Main Types of Medication With Anti-inflammatory Actions

Anti-inflammatory Components	Crosses BBB	Actions in the Brain
Antipsychotics	++	Dopamine receptor blockade (D2), ↑BDNF[18]
Aspirin	−/+	PG↓, TNF-α↓[19]
Celecoxib	++	COX-2↓, PG↓[18]
Cytostatics	−/+	Diverse, eg, for MTX: TNF-α↓[20]
Davunetide	++	TNF-α↓[18]
Estrogens	++	TNF-α↓, NO↓[21]
Fatty acids	++	Zinc↑, TNF-α↓, COX-2↓, IL-1↓[18]
Leptin	++	IL-4↓, IL-10↑, IFN-γ↓[22]
Macrolides/tetracyclines	++	IL-1β↓, NO↓[23], [94]
Melatonin	++	NO↓, IL-1β↓, TNF-α↓, NF-κβ↓[18]
Minocycline	++	Microglia inhibition, TNF-α↓[24]
Monoclonal antibodies	−/+	Inhibition of one specific component
NAC	++	IL-1β↓, TNF-α↓[25], [95]
Corticosteroids	−/+	Inhibition of many steps in innate and specific immune response
Transplantation adjuncts	−/+	IL-1/2/4↓

Sommer IE et al. Schizophr Bull 2014;40:181-91

Blandete funn

- Noen begrensninger ved utførte studier
  - Små utvalg
  - Uselekterte
  - Iavpotente legemidler

Kahn&Sommer. Mol Psychiatry 2015;20:84-97;
Khandaker GM et al. Lancet Psychiatry 2015;2:258-70.

Et mer potent valg

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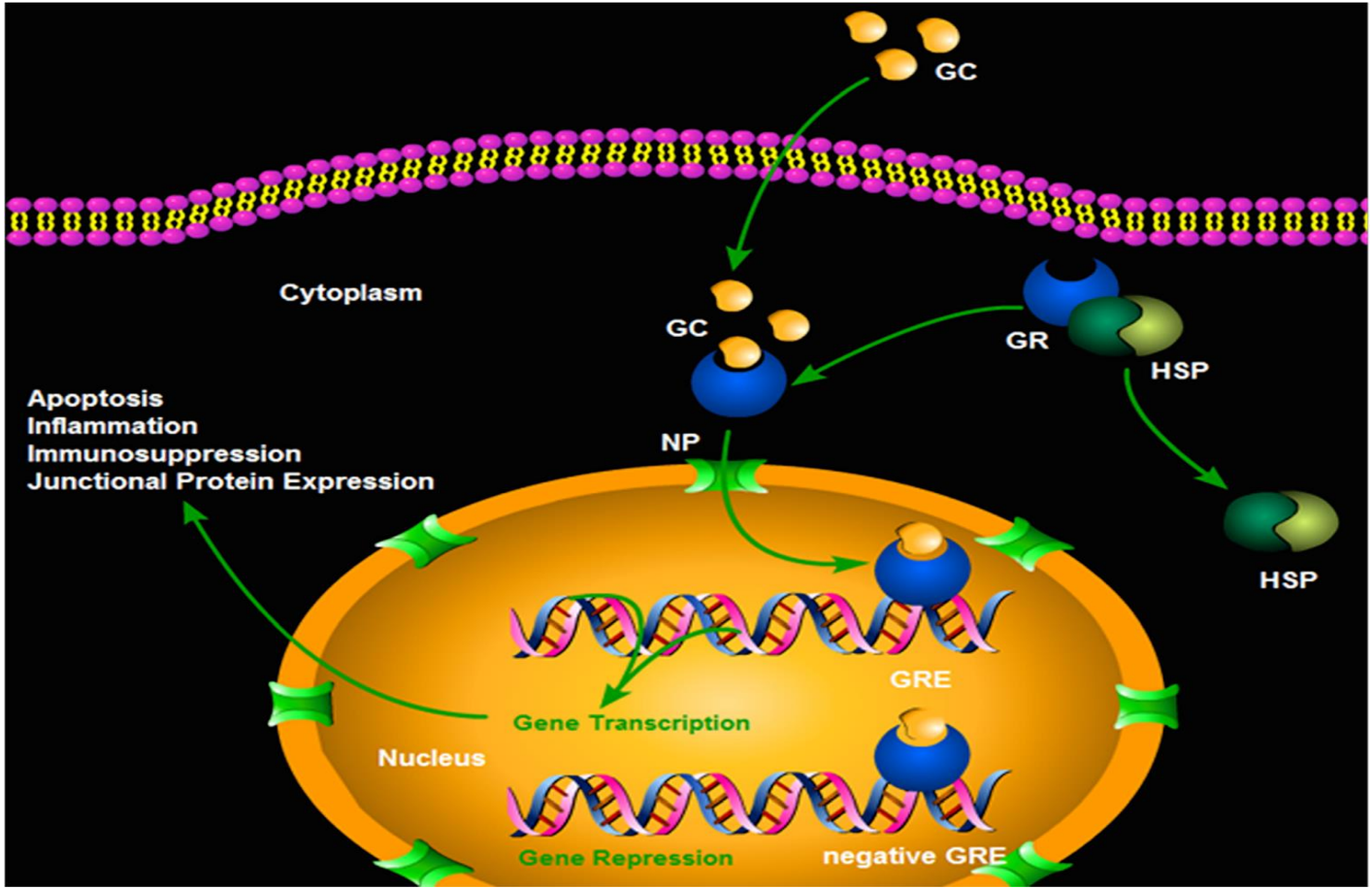
Sommer IE et al. Schizophr Bull 2014;40:181-91

Prednisolon

- Semisyntetisk derivat av kortisol, 4-5 x mer potent
- Genomiske og ikke-genomiske virkningsmekanismer: anti-inflammatoriske og immunsupressive effekter
- Krysser blood-hjerne barriæren
- Mange tiårs erfaring med preparatet


GC
Cytoplasm
GC
GR
HSP
Apoptosis
Inflammation
Immunosuppression
Junctional Protein Expression
NP
HSP
GRE
Gene Transcription
Nucleus
Gene Repression
negative GRE

Målsetninger

- Proof-of-concept
  - Kan tillegg av pednisolon ha gunstige effekter på
    - Symptomreduksjon
    - Kognisjon

- Identifisere inflammasjonsmarkører som predikerer respons

- Prospektivt måle hjerneinflammasjon med MR og sammenligne med perifere inflammasjonsmarkører og klinisk endring

Utfallsmål

- Primært utfallsmål:
  - Reduksjon av PANSS-skåre fra baseline til 6 uker

- Sekundære utfallsmål:
  - Reduksjon av PANSS-skåre etter 6 og 12 måneder
  - Reduksjon av PANSS subdomene-skårer
  - Bedring av kognitiv funksjon målt ved BACS
  - Bedring av GAF
  - Bedring av depresjon målt ved CDSS
  - Identifisering av immunparametre som predikerer effekt av immunsuppressiv behandling
  - Forekomst av bivirkninger og uønskede hendelser

Design

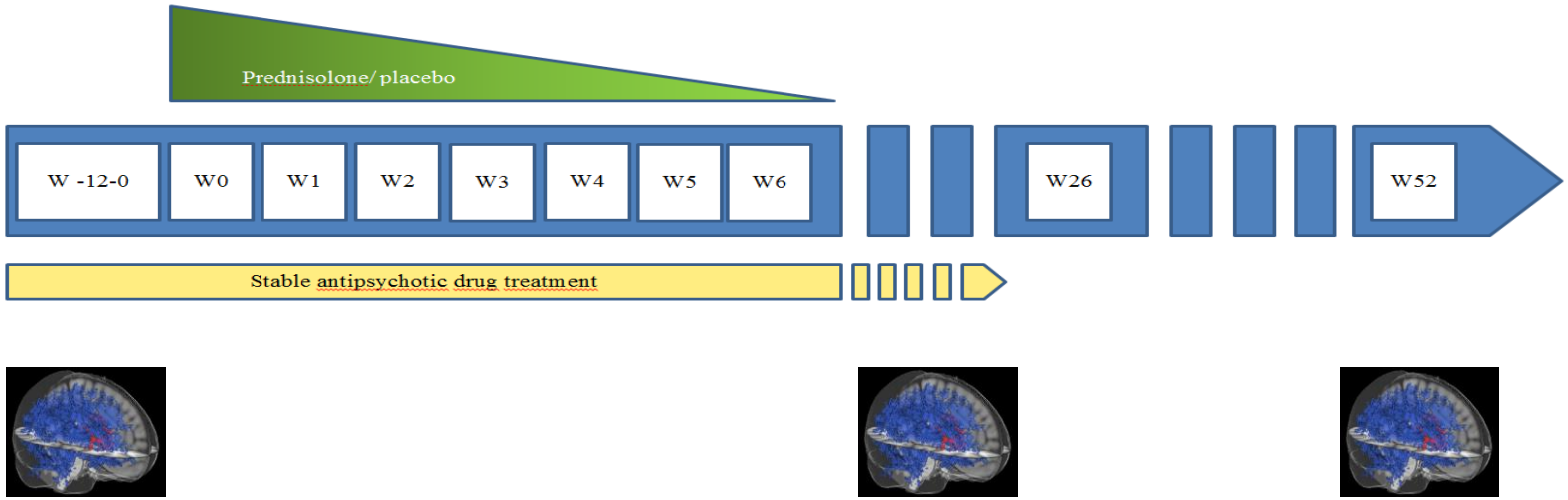
- Randomisert dobbelt-blind placebo-kontrollert add-on design.
- 6 uker med prednisolon/ placebo
- 1 års oppfølging
- N=90

Inklusjonskriterier

- Schizofreni-spektrum, < 5 års sykdomsvarighet
- Minimum total PANSS score 60.
- Pasienter som bruker stabil antipsykotisk medikasjon
- Plasma CRP ≥ 3.9 mg/L

Eksklusjonskriterier

- Kontraindikasjoner mot prednisolon
- Diabetes mellitus, alvorlig hjertesvikt, alvorlig osteoporose eller systemisk soppinfeksjon
- Body Mass Index (BMI) >27.5
- Pågående eller kronisk bruk av systemiske glukokortikosteroider
- Kronisk bruk av NSAIDS
- Graviditet/ amming.
- Samtidig bruk av visse interagerende medikamenter


Prednisolone/ placebo
W -12-0
W0
W1
W2
W3
W4
W5
W6
W26
W52
Stable antipsychotic drug treatment

Prednisolon - administrering

- *uke 1:*
  - dag 1-3: 40 mg/dag, fordelt på to inntak
  - dag 4-7: 30 mg/dag, fordelt på to inntak
- *uke 2:*
  - 25 mg/dag, fordelt på to inntak
- *uke 3:*
  - 20 mg/dag, fordelt på to inntak
- *uke 4:*
  - 15 mg/dag, fordelt på to inntak
- *uke 5:*
  - 10 mg/dag, inntak én gang daglig
- *uke 6:*
  - dag 1-3: 5 mg/dag, inntak én gang daglig
  - dag 4-7: på dag 5 og 7, 5 mg/dag, inntak én gang daglig, på dag 4 og 6 ingen tabletter.

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