Neuro-Inflammation in Schizophrenia and Autism

A Role for Minocycline?

Schizophrenia Risk Factors

Environmental Risks

-prenatal exposure to virus
-prenatal poor nutrition
-perinatal hypoxia
-psychotropic drug use
-psychological stress
-advanced paternal age
-birth order
-season of birth

Neurodegenerative Theories

-progressive loss of neuronal function
-loss of dendrites
-destruction of neuronal synapses
-neuronal cell death

Symptoms of Schizophrenia

Positive
Delusions, hallucinations, distortions/exaggerations in language and communication, disorganized speech, catatonic behavior, agitation

Negative
Blunted affect, emotional withdrawal, poor rapport, passivity, apathetic, alogia, anhedonia, avolition, difficulty with abstract thinking, lack of spontaneity

Cognitive
Difficulty: representing and maintaining goals, focusing/sustaining attention, information processing, prioritizing, problem solving

Affective
Depressed or anxious mood, guilt, tension, irritability, worry

Aggressive
Overt hostility, self-injurious behavior, impulsivity

Pathophysiology of Schizophrenia

a. Dopamine (DA)

i. Nigrostriatal Pathway: decreased DA-->extrapyramidal symptoms (EPS) and tardive dyskinesia
ii. Mesolimbic Pathway: increased DA-->positive sx and possibly aggressive sx
iii. Mesocortical Pathway: decreased DA-->negative, cognitive, affective sx
iv. Tubero-hypophyseal Pathway: decreased DA-->hyperprolactinemia

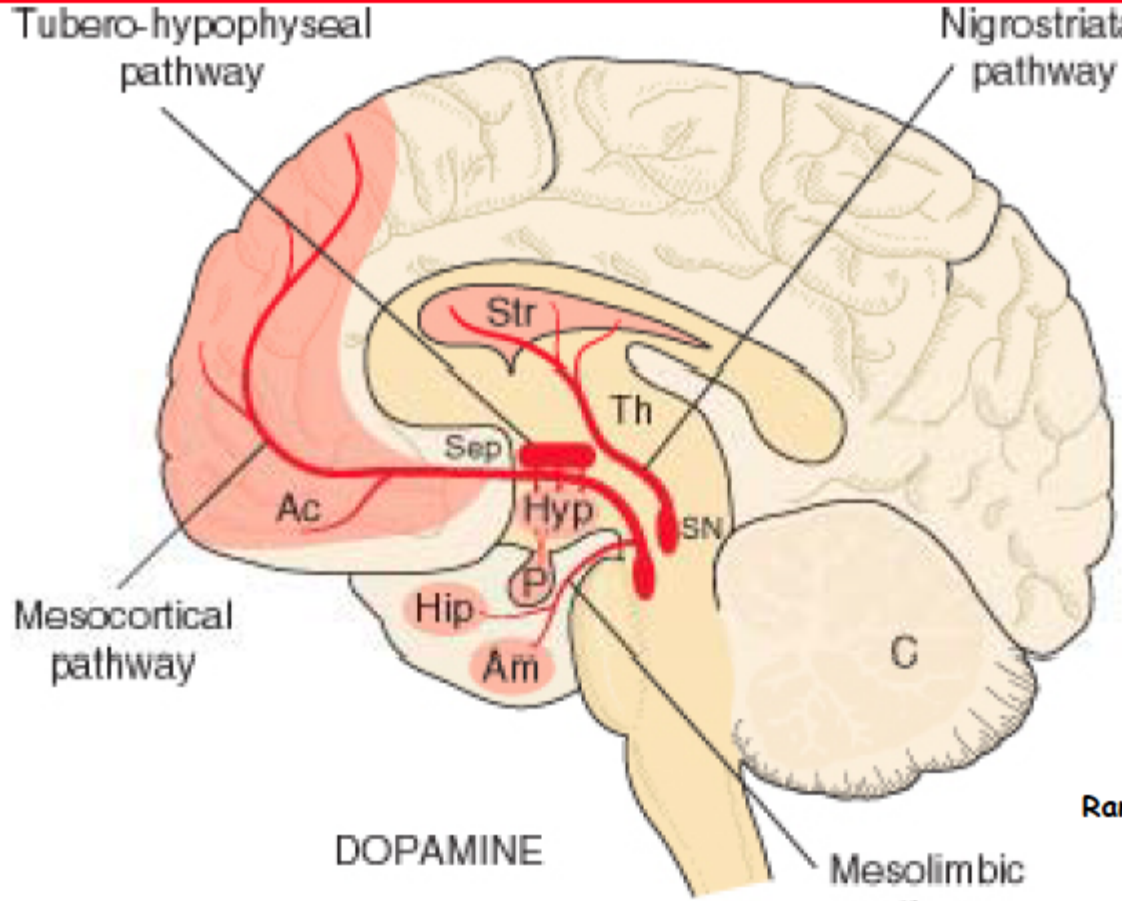
b. Glutamate

i. Decreased glutamate can have downstream effects causing DA hyperactivity in the mesolimbic pathway and hypoactivity in the mesocortical pathway

c. Inflammatory Pathway

i. Microglia have been shown to be more activated in schizophrenia
1. Microglia: macrophage cells of the central nervous system that regulate immune reactivity
a. Regulate cellular repair, and recruit immune cells into the brain for clearance of infection or cellular debris
b. Chronic or exaggerated microglial activation excessive secretion of pro-inflammatory factors
ii. Increase in pro-inflammatory factors
1. Interleukin-6, interleukin-1β, tumor necrosis factor-α, free radicals, nitric oxide

Dopaminergic pathways in the CNS



Rang et al. (2012) Fig. 38.3

Pathophysiology of Schizophrenia

a. Dopamine (DA)

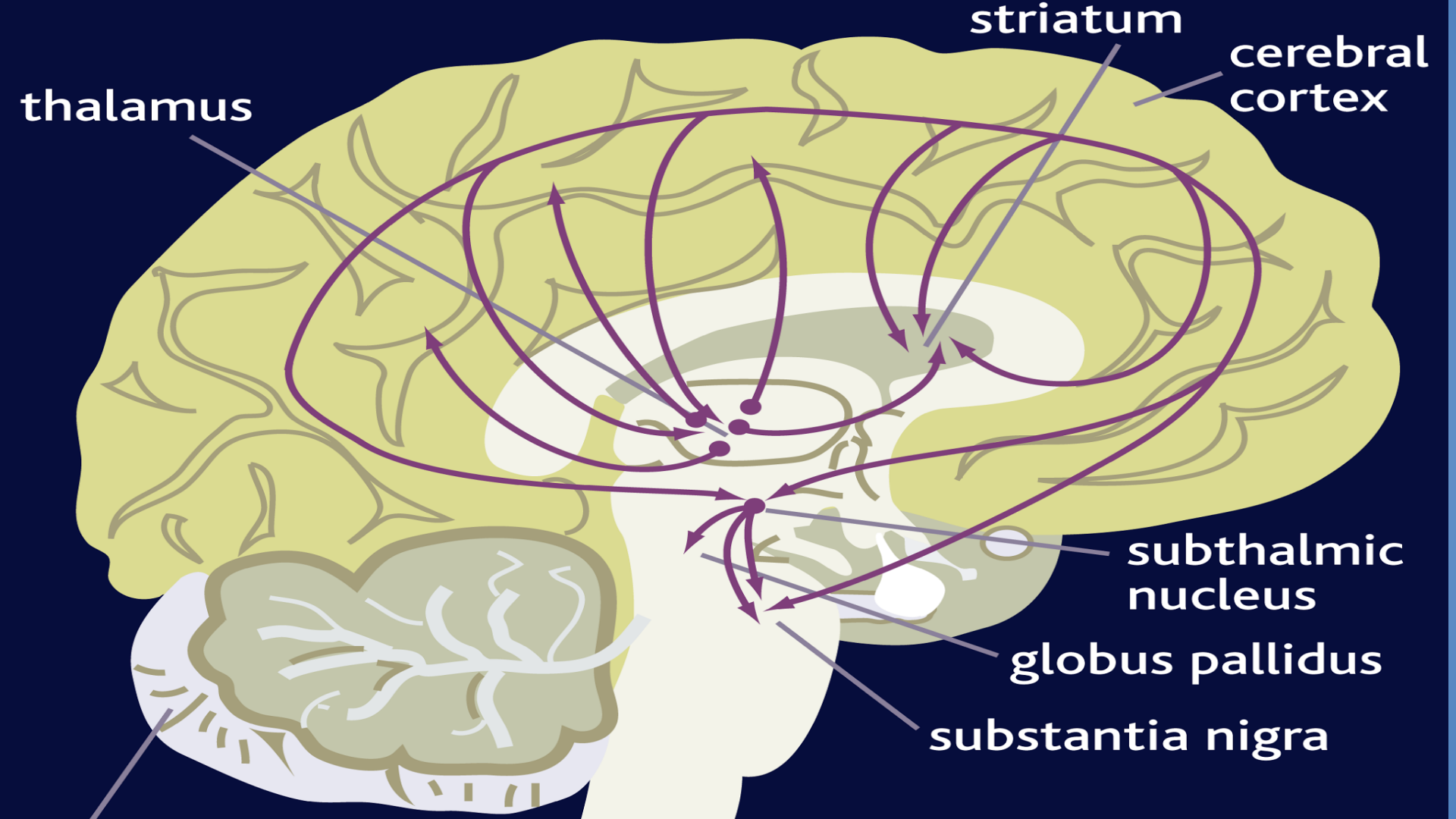
i. Nigrostriatal Pathway: decreased DA-->extrapyramidal symptoms (EPS) and tardive dyskinesia
ii. Mesolimbic Pathway: increased DA-->positive sx and possibly aggressive sx
iii. Mesocortical Pathway: decreased DA-->negative, cognitive, affective sx
iv. Tubero-hypophyseal Pathway: decreased DA-->hyperprolactinemia

b. Glutamate

i. Decreased glutamate can have downstream effects causing DA hyperactivity in the mesolimbic pathway and hypoactivity in the mesocortical pathway

c. Inflammatory Pathway

i. Microglia have been shown to be more activated in schizophrenia
1. Microglia: macrophage cells of the central nervous system that regulate immune reactivity
a. Regulate cellular repair, and recruit immune cells into the brain for clearance of infection or cellular debris
b. Chronic or exaggerated microglial activation excessive secretion of pro-inflammatory factors
ii. Increase in pro-inflammatory factors
1. Interleukin-6, interleukin-1β, tumor necrosis factor-α, free radicals, nitric oxide


striatum
cerebral cortex
thalamus
subthalmic nucleus
globus pallidus
substantia nigra

Current Treatment Options

a. The selection of an antipsychotic medication is frequently guided by the patient's previous experience with antipsychotics, including the degree of symptom response, past experience of side effects, and preferred route of medication administration

   i. First generation antipsychotics (FGAs)
      1. Primarily antagonize D2 receptors-->positive sx
   ii. Second generation antipsychotics (SGAs)
      1. Have affinity for multiple receptors-->positive and negative sx

b. There are no guideline recommendations for the treatment of negative symptoms

Antipsychotic Agents

First Generation Antipsychotics (FGAs)

Thorazine®	Chlorpromazine
Prolixin®	Fluphenazine
Haldol®	Haloperidol
Trilafon®	Perphenazine
Mellaril®	Thioridazine
Stelazine®	Trifluoperazine

Second Generation Antipsychotics (SGAs)

Solian®	Amisulpride*
Abilify®	Aripiprazole
Saphris®	Asenapine
Clozaril®	Clozapine
Fanapt®	Iloperidone
Latuda®	Lurasidone
Zyprexa®	Olanzapine
Invega®	Paliperidone
Lullan®	Perospirone*
Seroquel®	Quetiapine
Risperdal®	Risperidone
Geodon®	Ziprasidone

*Not approved in the United States

Minocycline

Description	Broad spectrum, second generation, lipophilic, tetracycline antibiotic
FDA indications	Acne, chlamydia, gonorrhea, meningitis, prosthetic joint infection, syphilis
Unlabeled uses	Rheumatoid arthritis, cellulitis
Research	Huntington's disease, Parkinson's disease, schizophrenia, amyotrophic lateral sclerosis, autism
Mechanism of action.	Inhibits 30s ribosomal protein synthesis in susceptible bacteria
Adult Dose	100-200mg/day depending on indication Max dose=400mg/day
Absorption	Well absorbed orally
Protein binding	70-75%
Metabolism	Hepatic to inactive metabolites
Half-life	Oral ranges from 11-22 hours
Excretion	Urine, feces
Renal impairment	CrCl <80 ml/min dose not to exceed 200mg/day
Hepatic impairment	Use with caution- no specific dose recommendations
Pregnancy category	D
Safety	Tooth discoloration, hepatic effects, autoimmune syndromes, CNS effects, tissue hyperpigmentation hypersensitivity reactions

Minocycline's Role in Schizophrenia

a. Glutamate effects

   i. Pathway: damaged glutamate NMDA receptors--> impaired glutamate transmission-->hypoglutamatergic states

   ii. Minocycline: enhances NMDA receptor activation

b. Microglia activation

   i. Pathway: increased microglia activation-->increase in pro-inflammatory factors

   ii. Minocycline: inhibits microglia activation

c. Apoptotic effects

   i. Pathway: vulnerability of apoptosis increased in schizophrenia

   ii. Minocycline: reduces apoptosis in neuronal cells

d. Antioxidant properties and free radical scavenger

   i. Pathway: Oxidative stress-->increases in reactive species of free radicals-->cellular dysfunction-->decreased antioxidant levels

   ii. Minocycline: prevent increases in production of reactive species of free radicals

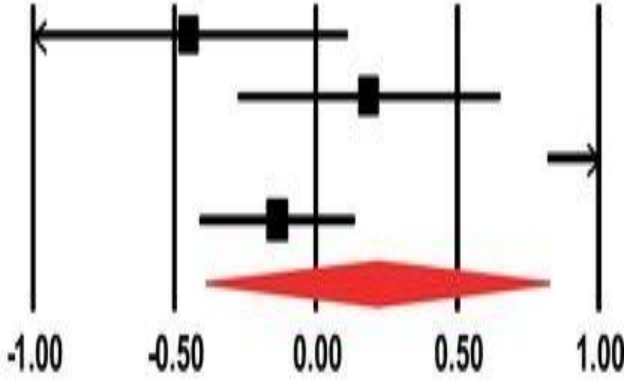
Potential Neurobiological Substrate of Negative Symptoms	Potential Therapeutic Mechanism of Minocycline
Impaired neurotransmission via NMDA receptors  *Damaged/malfunctioning NMDA receptors*	Enhances glutamatergic neurotransmission  *Functional NMDA receptor*
Increased neuroinflammation  *Activated microglia*	Reduces microglial activation  *Inactivated microglia*
 *Increased circulating cytokines*	Reduces circulating cytokines  *Decreased cytokines*

NMDA: N-methyl-D-aspartate

Minocycline augmentation

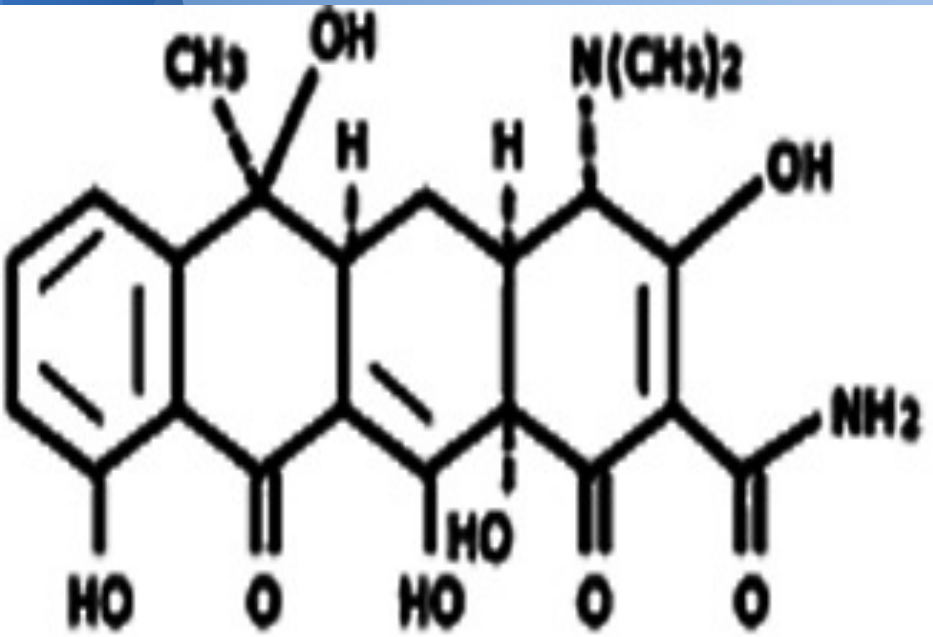
Study name	Hedges's g	p-Value	Sample size: minocycline	Sample size: placebo	duration of treatment
Levkovitz et al. 2010	-0.45	0.12	36	18	24
Chaudhry et al. 2012 Pakistan site	0.19	0.43	33	37	52
Chaudhry et al. 2012 Brazil site	1.73	0.00	13	11	52
Weiser et al. 2012	-0.14	0.33	100	100	16
	0.22	0.48			

Hedges's g and 95% CI

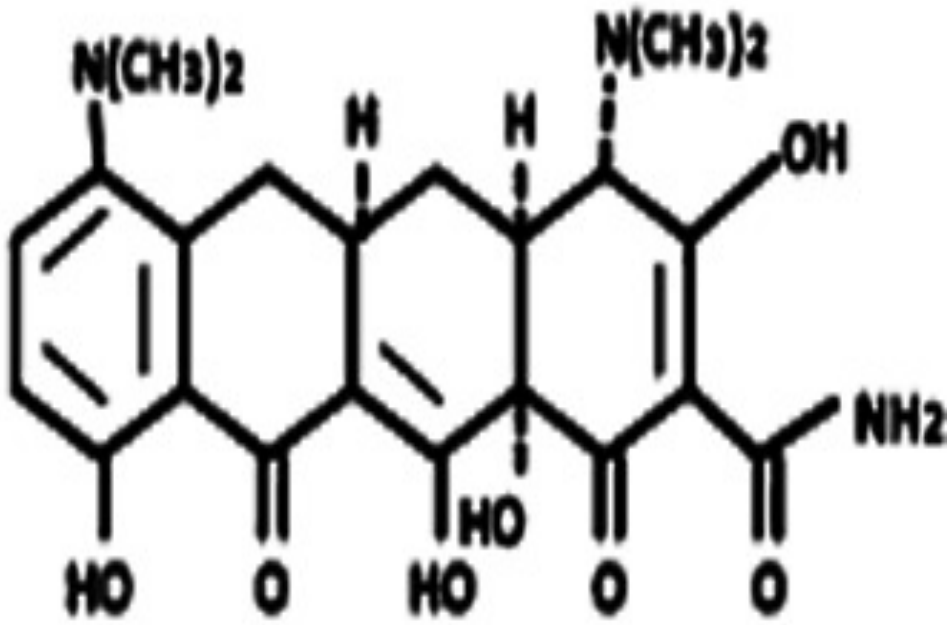


placebo minocycline

Minocycline in Autism Spectrum Disorders



Tetracycline



Minocycline

An Neuroinflammatory Model Linking Autism and Schizophrenia

Under normal conditions, inflammation is controlled by various homeostatic processes that limit or counteract inflammation once it has been induced by an environmental stimulus, *e.g.* infection. Such control mechanisms ensure that inflammatory processes efficiently remove invading pathogens and contribute to tissue repair and wound healing without placing noninfected, healthy, and unwounded tissue in jeopardy.

An Neuroinflammatory Model Linking Autism and Schizophrenia

Dysfunction of such surveillance mechanisms may lead to chronic inflammation, known from numerous pathological conditions such as rheumatoid arthritis, atherosclerosis, obesity, and diabetes.

An Neuroinflammatory Model Linking Autism and Schizophrenia

In the CNS, microglia and astrocytes are the major immunocompetent cells, which regulate both the induction and limitation of inflammatory processes.

An Neuroinflammatory Model Linking Autism and Schizophrenia

This is achieved through the synthesis of pro- and anti-inflammatory cytokines, up- or down-regulation of various cell surface receptors such as pathogen recognition receptors, cytokine receptors, and numerous receptors crucial for antigen presentation.

An Neuroinflammatory Model Linking Autism and Schizophrenia

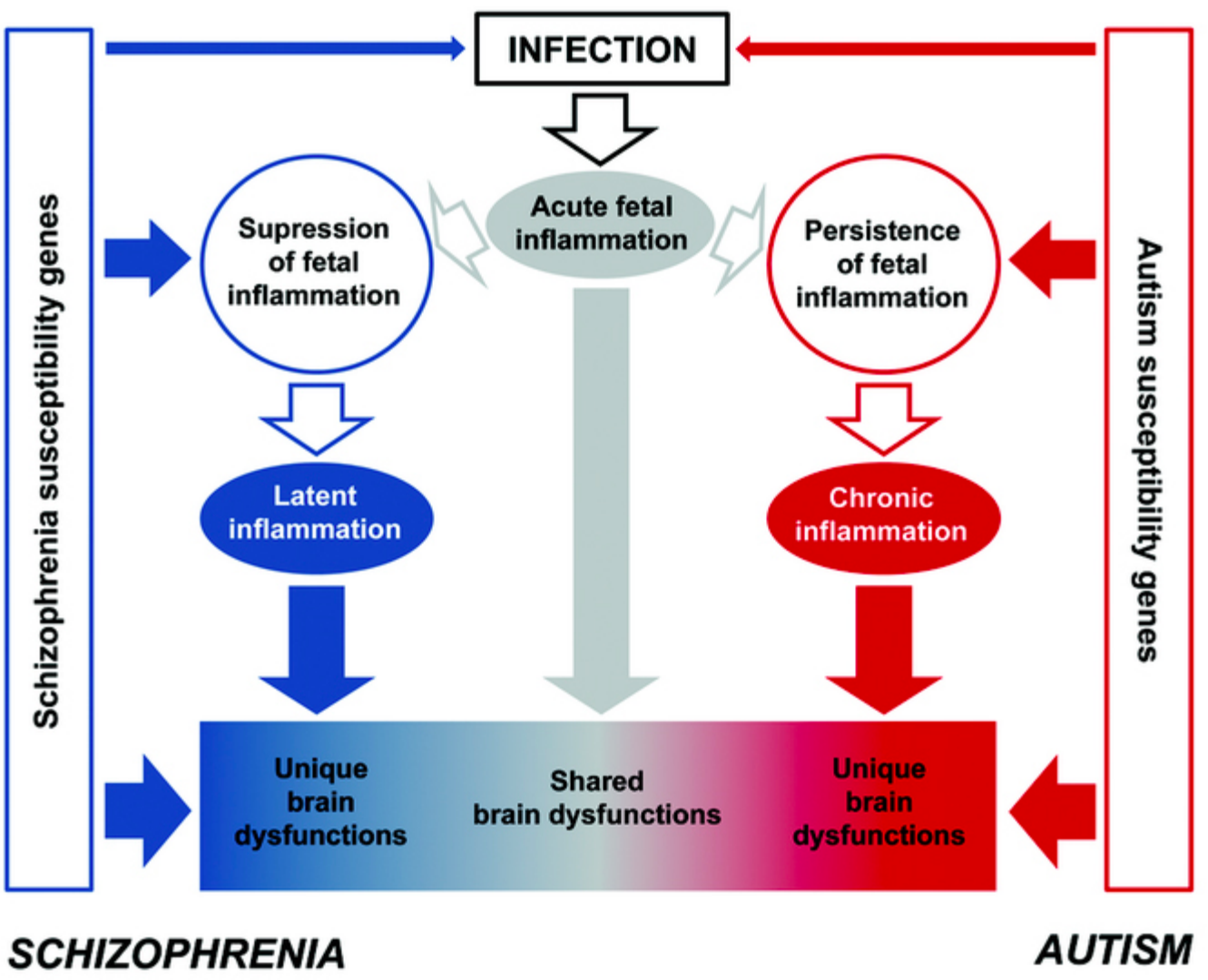
Microglia seem to play crucial roles in both neuronal protection and pathology and are often referred to as a “double-edged sword.”

On the one hand, they secrete neurotrophic factors pivotal for cellular repair and recruit immune cells into the brain for clearance of infection or cellular debris.

An Neuroinflammatory Model Linking Autism and Schizophrenia

On the other hand, chronic or exaggerated microglial activation has been linked to multiple neuroinflammatory and neurodegenerative diseases, including Parkinson's disease, multiple sclerosis, Alzheimer's disease, and Huntington's disease.

Thus, perinatal inflammation may simultaneously account for both shared and unique pathological features of schizophrenia and autism.


INFECTION
Schizophrenia susceptibility genes
Autism susceptibility genes
Supression of fetal inflammation
Acute fetal inflammation
Persistence of fetal inflammation
Latent inflammation
Chronic inflammation
Unique brain dysfunctions
Shared brain dysfunctions
Unique brain dysfunctions
SCHIZOPHRENIA
AUTISM

An Neuroinflammatory Model Linking Autism and Schizophrenia

Prenatal infection and inflammatory responses seem to play a significant role in the etiology of both schizophrenia and autism. This suggests that the pathogenesis of schizophrenia and autism may be fundamentally linked *via* prenatal inflammation.

An Neuroinflammatory Model Linking Autism and Schizophrenia

Acute neuroinflammation during early fetal development may be relevant for the induction of psychopathological and neuropathological phenotypes shared by schizophrenia and autism, whereas subsequent latent *versus* persistent inflammation may lead to phenotypic characteristics of schizophrenia *versus* autism, respectively.

An Neuroinflammatory Model Linking Autism and Schizophrenia

Autism but not schizophrenia seems to be characterized by relatively severe chronic inflammation, both in the periphery and in the CNS, although altered immune regulations have been implicated in both disorders.
Several recent studies corroborate the presence of ongoing systemic inflammation and neuroinflammation in autistic individuals.

An Neuroinflammatory Model Linking Autism and Schizophrenia

For example, a nearly 50-fold increase in TNF-αlevel was found in the cerebrospinal fluid (CSF) of autistic children, and severe inflammation is present in the brains of autistic patients from a broad range of ages, characterized by prominent activation of microglia and astroglia cells and enhanced proinflammatory cytokine and chemokine expression in multiple brain areas, including the cerebellum, cortex, and white matter tracts.

An Neuroinflammatory Model Linking Autism and Schizophrenia

Maternal infection during critical stages of pregnancy leads to acute cytokine-associated inflammation in the fetal system, including the fetal brain.

Acute neuroinflammation during early fetal brain development may negatively affect ongoing neurodevelopmental processes such as neuronal/glial cell differentiation, proliferation, migration, and survival.

Acute fetal neuroinflammation, together with its effects on early neurodevelopmental processes, may facilitate the development of psychopathological and neuropathological phenotypes shared by schizophrenia and autism.

An Neuroinflammatory Model Linking Autism and Schizophrenia

In contrast to the delayed onset of schizophrenia, overt symptoms of autism often begin as early as by the age of 6 mo and become established by age 2 or 3 y, coinciding with persistent neonatal neuroinflammation, so that enhanced expression of proinflammatory markers, including many cytokines, may exert a direct influence on postnatal brain functions relevant to the expression of autistic behavior by modulating learning and memory, anxiety-related behaviors, and social interaction.

An Neuroinflammatory Model Linking Autism and Schizophrenia

Hence, acute fetal neuroinflammation may be responsible for aberrant development of neural substrates of social behavior and cognition, emotional processing, sensorimotor gating, and certain executive functions, the disruption of which has been similarly implicated in schizophrenia and autism.

An Neuroinflammatory Model Linking Autism and Schizophrenia

Thus far the studies on minocycline use in ASDs are thin and highly preliminary, with no solid effects noted.
Anecdotal reports are increasing.
Further study seems warranted and judicious use may be helpful in clinical settings.
Given that this is used for acne treatment, it may be reasonable to consider it for ASDs.

Minocycline Mischief

Japanese Honey Trap Experiment with Minocycline as the variable…

Truly bizarre...

Male participant views the photo of a female partner on a computer display

Decision: Male participant
How much money should be given to the female partner (0–1300 yen, in increments of 100 yen)?

Offers nothing

Male participant receives 1300 yen
Female partner receives 1300 yen
Game Over

Offers all

The money at stake is tripled.
(1300 yen × 3 = 3900 yen)
In addition, the female partner has 1300 yen. Total: 5200 yen

Decision: Female partner
Take all the money (5200 yen) or split the money evenly with male participant?

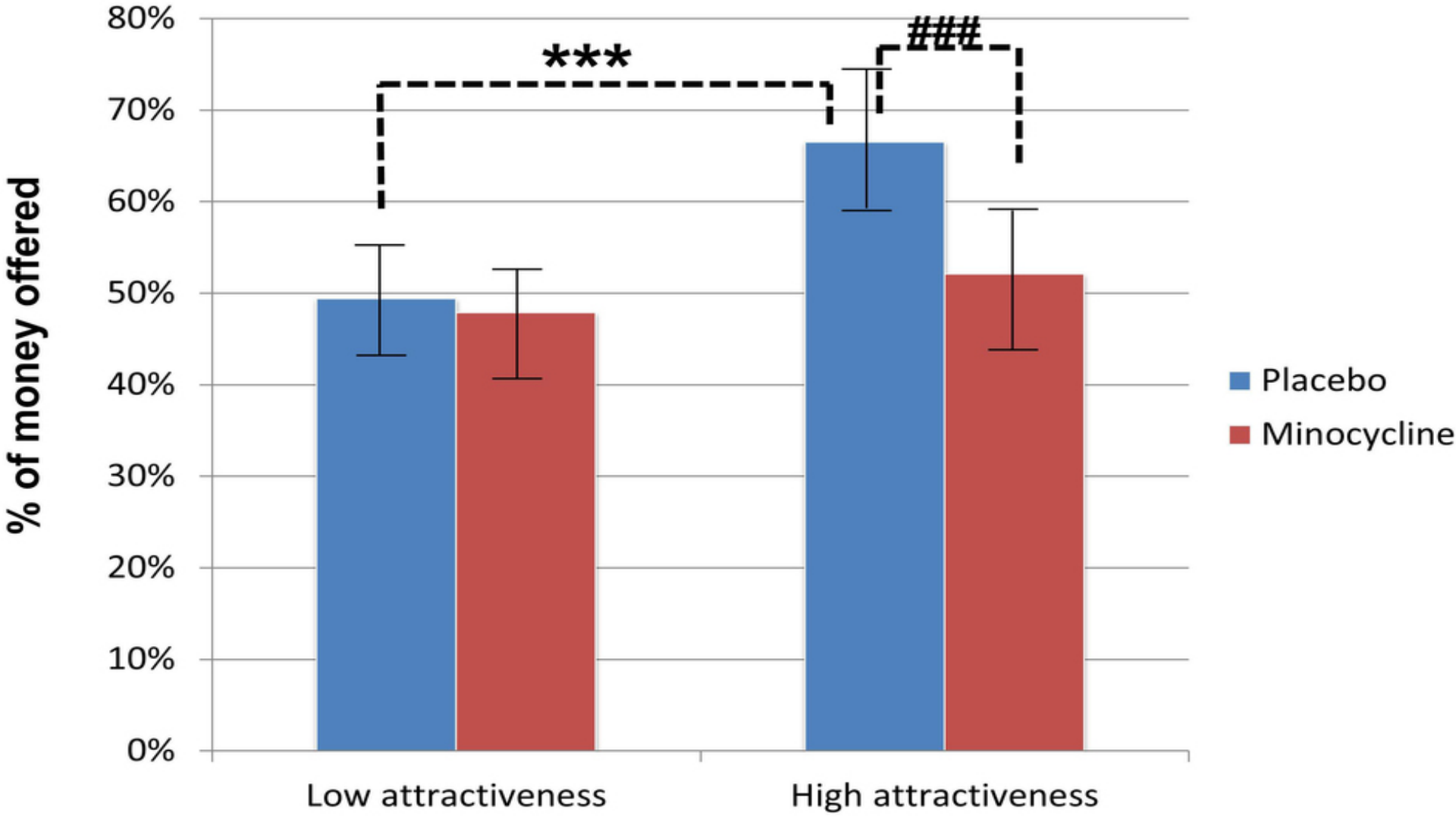
Take (Betray)

Male participant receives nothing
Female partner receives 5200 yen
Game Over

Female partner made this choice in advance

Split (Cooperate)

Male participant receives 2600 yen
Female partner receives 2600 yen
Game Over


80%
70%
60%
50%
40%
30%
20%
10%
0%
% of money offered
***
###
Placebo
Minocycline
Low attractiveness
High attractiveness