Douglas Dailey, L.Ac., BCB, BCN, QEEG-D
PO Box 2327, Santa Clara CA 950501■ (408) 984-3333 ■ mind@growing.com ■ www.growing.com/mind,
www.cortexercise.com

I developed this description, which is mostly theoretical, in order to explain why change was difficult for many clients, why neurofeedback was sometimes slow in implementing change, and why certain nutriceuticals had beneficial effects on these processes. The theory, based on my interpretation of the literature, suggests that neuroplasticity and change is dependent upon an immune mediated process that often strains the executive functions and leads to what I call "synaptic recidivism."

The Theory of Synaptic Recidivism

Neuroinflammation and neuroplasticity:

Perhaps the best discussion I have seen of this subject is by Filippo et al, 2008, in an article "Neuroinflammation and synaptic plasticity." [1]

> "For many years, the CNS has been considered to be immune-privileged, because, within its boundaries, there is an absence of any classical immune response to foreign antigens. Nevertheless, recent studies have challenged this view, and it is now well accepted that the nervous and immune systems are engaged in an intense bidirectional communication." [1]
>
> "Molecules that, classically, have been thought to exclusively mediate immune function (e.g. cytokines or major histocompatibility complex [MHC] molecules) have been found to actively modulate synaptic memory processes." [1]
>
> "It is thus possible to hypothesize that the combination of abnormal expression of inflammatory mediators occurring during CNS inflammation and other disease-specific abnormalities results in the impairment of synaptic plasticity and in the subsequent destabilization of neuronal networks." [1]
>
> "Indeed at low, 'physiological' levels, these immune mediators might be essential for the induction and maintenance of neuroplasticity, whereas, when overexpressed during a neuroinflammatory process, they might result in neurodegeneration and the impairment of synaptic plasticity." [1]

A www.pubmed.gov search for "neuroinflammation" OR "neuroinflammatory" retrieves over 2450 articles.

The immune (inflammatory) response involved in neuroplasticity involves oxidation and produces free radicals and reactive oxygen species (ROS). Glutathione (GSH) is the main protective antioxidant produced by cells. Glutathione is especially active in the nervous system and immune system. It is well described in an entry in Wikipedia [2]. Or you could search through the over 89,400 abstracts at PubMed.

"Glutathione depression" - 559 abstracts.
"Glutathione Alzheimer" - 294 abstracts.
"Glutathione schizophrenia" - 127 abstracts.
"Glutathione anxiety" - 58 abstracts.
"Glutathione autism" - 47 abstracts.
"Glutathione bipolar" - 43 abstracts.
"Glutathione addiction" - 33 abstracts.

"Glutathione depletion" returns over 6300 citations.
"Glutathione deficiency" returns over 5000 citations.

IDEA #1: Change (neuroplasticity) requires immune mediated inflammation. This inflammation is modulated largely by glutathione. Glutathione is depleted or deficient in many individuals (for a variety of interesting reasons). *Those conditions that are most difficult for us to treat are primarily those where the neurocellular defenses against inflammation are inadequate or overwhelmed.*

The delicate Von Economo neurons (VENs):

VENs are found in the anterior cingulate, the fronto-insular area, and have been recently found (2008) in the dorsolateral prefrontal cortex [3]. Possibly the single most important piece of literature on the VENs for NFB is the 2005 article by Allman et al, published in Trends in Cognitive Neuroscience [4].

> "The VENs develop late in ontogeny as well as phylogeny. They first appear in very small numbers in the 35th week of gestation and at birth only about 15% of the postnatal number are present. The adult number is attained by 4 years of age." [4]
>
> "Because of this late emergence in phylogeny, natural selection has had only a relatively short time to shape VEN functioning and integration with other cell populations. Consequently the VENs might be particularly vulnerable to dysfunction in a manner analogous to the propensity of humans to suffer lower back, hip and knee disorders as a consequence of the recent evolution of bipedal posture." [4]

VENs are only seen in the highest primates, in certain cetaceans, and in elephants - precisely those creatures with complex social organization, who sing communally, and who pass the mirror test for self-awareness. The Von Economo neurons may be the home of the executive functions as we know them. Because of their evolutionarily recent appearance, they lack robust genetic routines for combating stress, let alone the unexpected modern industrial assaults. The VENs may be the neurons most susceptible to significant oxidative damage.

The fronto-insular cortex with its VENs is instrumental in switching between the default mode, resting state, attention and executive networks. [5] Such network switching is known to be disturbed in Alzheimer's disease, anxiety, autism, bipolar disorder, depression, schizophrenia, and other disorders. [6] Many of these disturbances are the ones connected with neuroinflammation and glutathione described above.

The VENs are active in decision making under a high degree of uncertainty. They are also active in the experience of guilt, embarrassment, humor, trust, empathy, discrimination of mental state (of one's self and others), and intuition and snap decisions [4].

Of particular interest is that a disturbance of the VENs, as in autism, leads to an obsessive desire for the maintenance of sameness. Disturbances involving the VENs are "more likely to manifest themselves in unstructured situations" [4]. The tendency to make snap decisions in the service of sameness under cellular stress is, in my opinion, an issue which can impede clinical change and recovery from addictive behaviors, including addiction to one's own personality.

The VENs are the primary location outside of the gut where one finds serotonin 2b receptors. This gives new meaning to the expression 'gut feelings'. The serotonin 2b receptor may be also linked to the anticipation of punishment. The VEN dopamine D3 receptor may be linked to the anticipation of reward under conditions of uncertainty [4].

IDEA #2: The vulnerable VENs are 1) susceptible to oxidative stress and 2) disturbed in many conditions that are known to involve neuroinflammation. When dysfunctional, VENs can lead to resistance to change, aggravated during neuroplasticity. This might lead to what I call 'synaptic recidivism.'

N-Acetylcysteine and synaptic recidivism

At this point I ask myself, "Is there something that can reduce neuroinflammation and enable the VENs to negotiate real change and neuroplasticity?" Why do people wake up and say, "Today I will stop engaging in X" and then by the middle of the day they no longer see the wisdom of their decision?

The ancient (4000 BC) Vedic texts state, "The number one job of the physician is to keep his or her client from dying of addictions; and the number one addiction the client has is to his or her own personality." People have the opportunity to change for the better. They may be motivated. They may be trained with neurofeedback. But the neurons that fired together and wired together regain the day. This is synaptic recidivism.

As discussed above, chronic neurocognitive complaints are often accompanied by poorly regulated inflammation. Change (neuroplasticity) requires its own burst of inflammation. The very cells (VENs) that allow us to process embarrassment, social responsibility, intuition, trust and change are the first that succumb to the increased oxidative load of neuroplasticity.

In the following discussion I prefer to always consider immune dysfunction (and inflammation and change) as an issue involving self versus other. The other may be 1) what is growing inside the gut (remember serotonin 2b), 2) it may be the 'other' outside of us, and 3) it may even be parts of ourselves that we can no longer identify with because they have been dissociated.

If it is true that inflammation is a component of neuroplasticity and change, and if it is true that the additional oxidative load can cause the VENs to favor sameness, then it should be true that anything that calms the inflammation in the VENs will have the capacity to 1) normalize the network transformations, 2) reduce the etiological factors for many neurocognitive disorders, and especially 3) free the VENs to process higher human functions (as described above).

Recall that the main cellular moderator of the byproducts of inflammation is glutathione. Glutathione is often deficient in those suffering from neurocognitive disorders and their relatives. The most efficient exogenous substrate for glutathione is the safe and inexpensive amino acid N-acetylcysteine (NAC). Does NAC have any effect on conditions known to be mediated by neuroinflammation, network confusion, or VEN dysfunction?

Schizophrenia is known to have network switching dysfunction [7,8,9] and is known to be mediated by inflammation [10,11]. Enhancing glutathione through NAC supplementation has been shown to lead to rapid and significant cognitive improvement [11]. Enhancing the anti-inflammatory effects of glutathione through NAC supplementation has been shown to be similarly effective in bipolar disorder [12].

Resistance to change is the fundamental aspect of addiction. What are the observed effects of NAC and glutathione on addictive behaviors?

NAC has been shown effective in reducing cue-driven heroin and cocaine seeking [13,14] and in preventing cocaine relapse [14]. It has been shown to be of value in the treatment of pathological gambling [15] and even compulsive nail biting [16].

> "N-acetylcysteine (NAC) is a widely available nutraceutical with a variety of actions. As a precursor of cysteine and glutathione, it has antioxidant properties that may impact on mood and contribute to an effect on impulsivity and obsessive behavior. Via its additional effect on glutamate via the cystine-glutamate exchange system, NAC has been shown to mediate impulsivity in preclinical models of addiction, reduce craving, and cue extinction. Further, by boosting glutathione, NAC acts as a potent antioxidant and has been shown in two positive, large-scale randomized placebo-controlled trials to affect negative symptoms in schizophrenia and depression in bipolar disorder." [16].

The amelioration of alcohol and drug addiction through glutamatergic modulation (as with NAC) is well described in the 87 page review by Gass, et al, in 2009 [17].

> "...attenuation of glutamatergic transmission reduces drug reward, reinforcement, and relapse-like behavior.[17]

NAC's well documented effects in heavy metal poisoning and ischemic brain injury also make it seem like a natural for inclusion with neurofeedback in certain conditions [18,19].

IDEA #3: The notion that change (neuroplasticity) requires inflammation which then taxes the integrity of the VENs required for executive functions, is supported by the apparent effects of NAC on glutathione and its immune-modulating capacity.

Conclusion: I believe that the efficacy of neurofeedback rests on the twin pillars of neuroprotection and neuroplasticity. I have been attempting to understand how a client's genetics, epigenetics, diet and lifestyle can help or hinder the training of self-regulation. The enhancement of neuroplasticity itself (as opposed to neuroprotection described here) is a separate topic.

I apologize for any shortcomings in my interpreting of this literature. I welcome any corrections or comments.

Best wishes,

Douglas Dailey, L.Ac., BCB, BCN, QEEG-D.
Near San Francisco CA.
mind@growing.com.
www.cortexercise.com

---------- Citations ----------.

[1] Filippo MD, et al Neuroinflammation and synaptic plasticity: theoretical basis for a novel, immune-centred, therapeutic approach to neurological disorders. Trends in Pharmacological Sciences Vol.29 No.8, 2008.

[2] http://en.wikipedia.org/wiki/Glutathione.

[3] Fajardo C, et al (2008) - Von Economo neurons are present in the dorsolateral (dysgranular) prefrontal cortex of humans. Neuroscience Letters 435 (2008) 215–218.

[4] Allman JM, et al (2005) - Intuition and autism - A possible role for Von Economo neurons. Trends in Cognitive Sciences Vol.9 No.8 August 2005.

[5] Sridharan D, et al (2008) - A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. PNAS, Aug 26, 2008. Vol 105 No 34.

[6] Broyd SJ, et al (2009) - Default-mode brain dysfunction in mental disorders - A systematic review. Neuroscience and Biobehavioral Reviews 33 (2009) 279–296.

[7] Whitfield-Gabrieli S, et al (2009) - Hyperactivity and hyperconnectivity of the default network in schizophrenia and in first degree relatives. PNAS, Jan 27, 2009. Vol 106 No 4, p1279 -1284.

[8] Garrity AG, et al (2007) - Aberrant default mode functional connectivity in schizophrenia. Am J Psychiatry 2007; 164:450–457.

[9] Williamson P (2007) - Are anticorrelated networks in the brain relevant to schizophrenia. Schizophrenia Bulletin vol. 33 no. 4 pp. 994–1003, 2007.

[10] Doorduin J, et al (2009) - Neuroinflammation in schizophrenia-related psychosis: a PET study. Nucl Med. 2009 Nov;50(11):1801-7.

[11] Berk M, et al (2008) - N-acetyl cysteine as a glutathione precursor for schizophrenia - A double-blind, randomized, placebo-controlled trial. Biol Psychiatry 2008, 64:361-368.

[12] Berk M, et al (2008) - N-acetyl cysteine for depressive symptoms in bipolar disorder - A double-blind randomized placebo-controlled trial. Biol Psychiatry 2008;64:468-475.

[13] Zhou W, et al (2007) - N-acetylcysteine reduces extinction responding and induces enduring reductions in cue- and heroin-induced drug-seeking. Biol Psychiatry. 2008 February 1; 63(3): 338–340.

[14] Baker DA, et al (2003) - Neuroadaptations in cystine-glutamate exchange underlie cocaine relapse. Nature Neuroscience Vol 6, Number 7, July 2003.

[15] Grant JE, et al (2007) - N-acetyl cysteine, a glutamate-modulating agent, in the treatment of pathological gambling - A pilot study. Biol Psychiatry 2007;62:652–657.

[16] Berk M, et al (20090 - Nail-biting stuff? The effect of N-acetyl cysteine on nail-biting. CNS Spectr. 2009 Jul;14(7):357-60.

[17] Gass JT, et al (2008) - Glutamatergic substrates of drug addiction and alcoholism. Biochem Pharmacol. 2008 January 1; 75(1): 218–265.

[18] Ballatori N, et al (1998) - N-acetylcysteine as an antidote in methylmercury poisoning. Environmental Health Perspectives Volume 106, Number 5, May 1998.

[19] Cuzzocrea S, et al (2000) - Beneficial effects of n-acetylcysteine on ischaemic brain injury. British Journal of Pharmacology (2000) 130, 1219 - 1226.

Abstracts

Trends Pharmacol Sci. 2008 Aug;29(8):402-12. Epub 2008 Jul 9.

Neuroinflammation and synaptic plasticity: theoretical basis for a novel, immune-centred, therapeutic approach to neurological disorders.

Di Filippo M, Sarchielli P, Picconi B, Calabresi P.

Clinica Neurologica, Università degli Studi di Perugia, Perugia, Italy.

The fascinating capacity that the central nervous system (CNS) has for encoding and retaining memories is thought to be based on activity-dependent forms of synaptic plasticity. The CNS and the immune systems are known to be engaged in an intense bidirectional crosstalk, and glial cells are now viewed as a crucial third element of the synapse. In this opinion article, we review the principal mechanisms by which the immune system, and in particular immune diffusible mediators, influences synaptic transmission and the induction of brain plastic phenomena. Thereafter, we consider the potential implications of inflammation-related overexpression of diffusible mediators in the disruption of synaptic plastic processes

and neuronal networks functioning during human neurological diseases. Finally, we propose that a more accurate characterization of the mechanisms underlying the immune-mediated control of synaptic plasticity could represent, in the future, the basis for the development of a novel immune-centred therapeutic approach to neurological disorders.

http://www.ncbi.nlm.nih.gov/pubmed/18617277

Neurosci Lett. 2008 Apr 25;435(3):215-8. Epub 2008 Mar 4.

Von Economo neurons are present in the dorsolateral (dysgranular) prefrontal cortex of humans.

Fajardo C, Escobar MI, Buriticá E, Arteaga G, Umbarila J, Casanova MF, Pimienta H.

Centro de Estudios Cerebrales, Facultad de Salud, Universidad del Valle, Cali, Valle, Colombia.

Von Economo neurons (VENs), also known as spindle cells, have been described in layer V of the anterior cingulate (BA 24) and frontoinsular cortex (FI) of humans and other great apes. In the present study we used immunohistochemistry against two specific neuronal markers (NeuN and MAP2) in order to establish the presence of these cell types in Brodmann area 9 (BA 9) of the human prefrontal cortex. We evaluated tissue samples of eight human postmortem brains (age range 26-50) from BAs 9, 24, 4, 46, 45, 10 and 17. We identified a group of cells with similar morphology to that previously described for VENs in all specimens of BA 9 examined, albeit less frequently than in BA 24. This is the first description of this cell type in a human brain area with well developed granular layers (BA 9).

http://www.ncbi.nlm.nih.gov/pubmed/18355958

Trends Cogn Sci. 2005 Aug;9(8):367-73.

Intuition and autism: a possible role for Von Economo neurons.

Allman JM, Watson KK, Tetreault NA, Hakeem AY.

Division of Biology, California Institute of Technology, Pasadena, CA 91125, USA. cebus@caltech.edu

Von Economo neurons (VENs) are a recently evolved cell type which may be involved in the fast intuitive assessment of complex situations. As such, they could be part of the circuitry supporting human social networks. We propose that the VENs relay an output of fronto-insular and anterior cingulate cortex to the parts of frontal and temporal cortex associated with theory-of-mind, where fast intuitions are melded with slower, deliberative judgments. The VENs emerge mainly after birth and increase in number until age 4 yrs. We propose that in autism spectrum disorders the VENs fail to develop normally, and that this failure might be partially responsible for the associated social disabilities that result from faulty intuition.

http://www.ncbi.nlm.nih.gov/pubmed/16002323

Proc Natl Acad Sci U S A. 2008 Aug 26;105(34):12569-74. Epub 2008 Aug 22.

A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks.

Sridharan D, Levitin DJ, Menon V.

Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA 94305, USA. dsridhar@stanford.edu

Cognitively demanding tasks that evoke activation in the brain's central-executive network (CEN) have been consistently shown to evoke decreased activation (deactivation) in the default-mode network (DMN). The neural mechanisms underlying this switch between activation and deactivation of large-scale brain networks remain completely unknown. Here, we use functional magnetic resonance imaging (fMRI) to investigate the mechanisms underlying switching of brain networks in three different experiments. We first examined this switching process in an auditory event segmentation task. We observed significant activation of the CEN and deactivation of the DMN, along with activation of a third network comprising the right fronto-insular cortex (rFIC) and anterior cingulate cortex (ACC), when participants perceived salient auditory event boundaries. Using chronometric techniques and Granger causality analysis, we show that the rFIC-ACC network, and the rFIC, in particular, plays a critical and causal role in switching between the CEN and the DMN. We replicated this causal connectivity pattern in two additional experiments: (i) a visual attention "oddball" task and (ii) a task-free resting state. These results indicate that the rFIC is likely to play a major role in switching between distinct brain networks across task paradigms and stimulus modalities. Our findings have important implications for a unified view of network mechanisms underlying both exogenous and endogenous cognitive control.

http://www.ncbi.nlm.nih.gov/pubmed/18723676

Free full text: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2527952/?tool=pubmed

Neurosci Biobehav Rev. 2009 Mar;33(3):279-96. Epub 2008 Sep 9.

Default-mode brain dysfunction in mental disorders: a systematic review.

Broyd SJ, Demanuele C, Debener S, Helps SK, James CJ, Sonuga-Barke EJ.

Institute for Disorders of Impulse & Attention, Developmental Brain-Behaviour Laboratory, School of Psychology, University of Southampton, UK. s.broyd@soton.ac.uk

In this review we are concerned specifically with the putative role of the default-mode network (DMN) in the pathophysiology of mental disorders. First, we define the DMN concept with regard to its neuro-anatomy, its functional organisation through low frequency neuronal oscillations, its relation to other recently discovered low frequency resting state networks, and the cognitive functions it is thought to serve. Second, we introduce methodological and analytical issues and challenges. Third, we describe putative mechanisms proposed to link DMN abnormalities and mental disorders. These include interference by network activity during task performance, altered patterns of antagonism between task specific and non-specific elements, altered connectively and integrity of the DMN, and altered psychological functions served by the network DMN. Fourth, we review the empirical literature systematically. We relate DMN dysfunction to dementia, schizophrenia, epilepsy, anxiety and depression, autism and attention deficit/hyperactivity disorder drawing out common and unique elements of the disorders. Finally, we provide an integrative overview and highlight important challenges and tasks for future research.

http://www.ncbi.nlm.nih.gov/pubmed/18824195

Proc Natl Acad Sci U S A. 2009 Jan 27;106(4):1279-84. Epub 2009 Jan 21.

Hyperactivity and hyperconnectivity of the default network in schizophrenia and in first-degree relatives of persons with schizophrenia.

Whitfield-Gabrieli S, Thermenos HW, Milanovic S, Tsuang MT, Faraone SV, McCarley RW, Shenton ME, Green AI, Nieto-Castanon A, LaViolette P, Wojcik J, Gabrieli JD, Seidman LJ.

Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, MA 02139, USA. swg@mit.edu

We examined the status of the neural network mediating the default mode of brain function, which typically exhibits greater activation during rest than during task, in patients in the early phase of schizophrenia and in young first-degree relatives of persons with schizophrenia. During functional MRI, patients, relatives, and controls alternated between rest and performance of working memory (WM) tasks. As expected, controls exhibited task-related suppression of activation in the default network, including medial prefrontal cortex (MPFC) and posterior cingulate cortex/precuneus. Patients and relatives exhibited significantly reduced task-related suppression in MPFC, and these reductions remained after controlling for performance. Increased task-related MPFC suppression correlated with better WM performance in patients and relatives and with less psychopathology in all 3 groups. For WM task performance, patients and relatives had greater activation in right dorsolateral prefrontal cortex (DLPFC) than controls. During rest and task, patients and relatives exhibited abnormally high functional connectivity within the default network. The magnitudes of default network connectivity during rest and task correlated with psychopathology in the patients. Further, during both rest and task, patients exhibited reduced anticorrelations between MPFC and DLPFC, a region that was hyperactivated by patients and relatives during WM performance. Among patients, the magnitude of MPFC task suppression negatively correlated with default connectivity, suggesting an association between the hyperactivation and hyperconnectivity in schizophrenia. Hyperactivation (reduced task-related suppression) of default regions and hyperconnectivity of the default network may contribute to disturbances of thought in schizophrenia and risk for the illness.

http://www.ncbi.nlm.nih.gov/pubmed/19164577

Free Full Text: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2633557/?tool=pubmed

Am J Psychiatry. 2007 Mar;164(3):450-7.

Aberrant "default mode" functional connectivity in schizophrenia.

Garrity AG, Pearlson GD, McKiernan K, Lloyd D, Kiehl KA, Calhoun VD.

Trinity College, Hartford, CT, USA.

OBJECTIVE: The "default mode" has been defined as a baseline condition of brain function and is of interest because its component brain regions are believed to be abnormal in schizophrenia. It was hypothesized that the default mode network would show abnormal activation and connectivity in patients with schizophrenia. METHOD: Patients with schizophrenia (N=21) and healthy comparison subjects (N=22) performed an auditory oddball task during functional magnetic resonance imaging (fMRI). Independent component analysis was used to identify the default mode component. Differences in the spatial and temporal aspects of the default mode network were examined in patients versus comparison subjects. RESULTS: Healthy comparison subjects and patients had significant spatial differences in the default mode network, most notably in the frontal, anterior cingulate, and parahippocampal gyri. In addition, activity in patients in the medial frontal, temporal, and cingulate gyri correlated with severity of positive symptoms. The patients also showed significantly higher frequency fluctuations in the temporal evolution of the default mode. CONCLUSIONS: Schizophrenia is associated with altered temporal frequency and spatial location of the default mode network. The authors hypothesized that this network may be under- or overmodulated by key regions, including the anterior and posterior cingulate cortex. In addition, the altered temporal fluctuations in patients may result from a change in the connectivity of these regions with other brain networks.

http://www.ncbi.nlm.nih.gov/pubmed/17329470

Free Full Text: http://ajp.psychiatryonline.org/cgi/content/full/164/3/450

Schizophr Bull. 2007 Jul;33(4):994-1003. Epub 2007 May 10.

Are anticorrelated networks in the brain relevant to schizophrenia?

Williamson P.

Tanna Schulich Chair in Neuroscience and Mental Health, Schulich School of Medicine, University of Western Ontario, London, Canada. williams@uwo.ca

Most models of schizophrenia are based on basal ganglia-thalamocortical (BGTC) neuronal circuits or brain structures that project to them. Two new neuronal networks have been described which include many of the brain regions associated with BGTC neuronal circuits. These networks have been characterized with a new brain-imaging technique based on low-frequency fluctuations of the blood oxygen level-dependent (BOLD) signal. The new network associated with attention-demanding tasks is referred to as the task-related network and the network associated with stimulus-independent thought during the resting state is referred to as the default network. The 2 networks have been proposed to be negatively correlated or anticorrelated. This article critically reviews the rationale for these anticorrelated networks, the technique with which they are characterized, and preliminary findings in schizophrenia and other neuropsychiatric disorders. Regions associated with the default network overlap with regions important in motivation and are activated by memory retrieval, auditory hallucinations, and ketamine. Task-related networks are necessary for performance of neurocognitive tasks on which schizophrenic patients often perform poorly. It is concluded that anticorrelated networks can be viewed as complementary ways of understanding self-monitoring and task performance which extend present models of schizophrenia based on BGTC circuits. However, there are some limitations with regard the present understanding of brain structures involved in self-monitoring and the lack of asymmetry in the network which may mediate stimulus-independent thought. Further investigations of the default network assessed by low-frequency fluctuations in the BOLD signal seem warranted.

http://www.ncbi.nlm.nih.gov/pubmed/7493957

Free Full Text http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2632338/?tool=pubmed

J Nucl Med. 2009 Nov;50(11):1801-7. Epub 2009 Oct 16.

Neuroinflammation in schizophrenia-related psychosis: a PET study.

Doorduin J, de Vries EF, Willemsen AT, de Groot JC, Dierckx RA, Klein HC.

Department of Nuclear Medicine and Molecular Imaging, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands. j.doorduin@ngmb.umcg.nl

Schizophrenia is a chronic and disabling brain disease characterized by psychotic episodes with unknown etiology. It is suggested that neuroinflammation plays a role in the pathophysiology of schizophrenia. Neuroinflammation is characterized by the activation of microglia cells, which show an increase in the expression of the peripheral benzodiazepine receptor. The isoquinoline (R)-N-(11)C-methyl-N-(1-methylpropyl)-1-(2-chlorophenyl)isoquinoline-3-carboxamid e ((11)C-(R)-PK11195) is a peripheral benzodiazepine receptor ligand that can be used for the imaging of activated microglia cells, and thus neuroinflammation, with PET. We hypothesized that neuroinflammation would be more profound in schizophrenic patients during psychosis, and it was therefore investigated whether neuroinflammation

was present in patients within the schizophrenia spectrum who were in a psychotic phase. METHODS: Seven patients within the schizophrenia spectrum who were recovering from psychosis were included. Recovering psychosis was defined by a score of 5 or more on 1 item of the positive scale of the positive and negative symptoms scale (PANSS) or a score of 4 on 2 items. The patients were compared with 8 age-matched healthy volunteers. Dynamic 60-min PET scans were acquired after the injection of (11)C-(R)-PK11195. All subjects underwent T1- and T2-weighted MRI, and the scans were visually examined for abnormalities and used for anatomic coregistration in data analysis. The PET data were analyzed with a 2-tissue-compartment model to calculate the binding potential, using the metabolite-corrected plasma curve as input. RESULTS: A significantly higher binding potential of (11)C-(R)-PK11195, indicative of neuroinflammation, was found in the hippocampus of schizophrenic patients than in healthy volunteers (2.07 +/- 0.42 vs. 1.37 +/- 0.30; P = 0.004). A nonsignificant 30% higher (11)C-(R)-PK11195 binding potential was found in the whole-brain gray matter of schizophrenic patients. The MR images did not reveal any visual abnormalities. CONCLUSION: The present study suggests that focal neuroinflammation may play an important role in schizophrenia during psychosis.

http://www.ncbi.nlm.nih.gov/pubmed/19837763

Biol Psychiatry. 2008 Sep 1;64(5):361-8. Epub 2008 Apr 23.

N-acetyl cysteine as a glutathione precursor for schizophrenia--a double-blind, randomized, placebo-controlled trial.

Berk M, Copolov D, Dean O, Lu K, Jeavons S, Schapkaitz I, Anderson-Hunt M, Judd F, Katz F, Katz P, Ording-Jespersen S, Little J, Conus P, Cuenod M, Do KQ, Bush AI.

The Mental Health Research Institute of Victoria, Parkville, Australia.

BACKGROUND: Brain glutathione levels are decreased in schizophrenia, a disorder that often is chronic and refractory to treatment. N-acetyl cysteine (NAC) increases brain glutathione in rodents. This study was conducted to evaluate the safety and effectiveness of oral NAC (1 g orally twice daily [b.i.d.]) as an add-on to maintenance medication for the treatment of chronic schizophrenia over a 24-week period. METHODS: A randomized, multicenter, double-blind, placebo-controlled study. The primary readout was change from baseline on the Positive and Negative Symptoms Scale (PANSS) and its components. Secondary readouts included the Clinical Global Impression (CGI) Severity and Improvement scales, as well as general functioning and extrapyramidal rating scales. Changes following a 4-week treatment discontinuation were evaluated. One hundred forty people with chronic schizophrenia on maintenance antipsychotic medication were randomized; 84 completed treatment. RESULTS: Intent-to-treat analysis revealed that subjects treated with NAC improved more than placebo-treated subjects over the study period in PANSS total [-5.97 (-10.44, -1.51), p = .009], PANSS negative [mean difference -1.83 (95% confidence interval: -3.33, -.32), p = .018], and PANSS general [-2.79 (-5.38, -.20), p = .035], CGI-Severity (CGI-S) [-.26 (-.44, -.08), p = .004], and CGI-Improvement (CGI-I) [-.22 (-.41, -.03), p = .025] scores. No significant change on the PANSS positive subscale was seen. N-acetyl cysteine treatment also was associated with an improvement in akathisia (p = .022). Effect sizes at end point were consistent with moderate benefits. CONCLUSIONS: These data suggest that adjunctive NAC has potential as a safe and moderately effective augmentation strategy for chronic schizophrenia.

http://www.ncbi.nlm.nih.gov/pubmed/18436195

Biol Psychiatry. 2008 Sep 15;64(6):468-75. Epub 2008 Jun 5.

N-acetyl cysteine for depressive symptoms in bipolar disorder--a double-blind randomized placebo-controlled trial.

Berk M, Copolov DL, Dean O, Lu K, Jeavons S, Schapkaitz I, Anderson-Hunt M, Bush AI.

The Mental Health Research Institute of Victoria, Victoria, Australia.

BACKGROUND: Treatment-resistant subthreshold depression is a major problem in bipolar disorder. Both depression and bipolar disorder are complicated by glutathione depletion. We hypothesized that treatment with N-acetyl cysteine (NAC), a safe, orally bioavailable precursor of glutathione, may improve the depressive component of bipolar disorder. METHODS: A randomized, double-blind, multicenter, placebo-controlled study of individuals (n = 75) with bipolar disorder in the maintenance phase treated with NAC (1 g twice daily) adjunctive to usual medication over 24 weeks, with a 4-week washout. The two primary outcomes were the Montgomery Asberg Depression Rating Scale (MADRS) and time to a mood episode. Secondary outcomes included the Bipolar Depression Rating Scale and 11 other ratings of clinical status, quality of life, and functioning. RESULTS: NAC treatment caused a significant improvement on the MADRS (least squares mean difference [95% confidence interval]: -8.05 [-13.16, -2.95], p = .002) and most secondary scales at end point. Benefit was evident by 8 weeks on the Global Assessment of Functioning Scale and Social and Occupational Functioning Assessment Scale and at 20 weeks on the MADRS. Improvements were lost after washout. There was no effect of NAC on time to a mood episode (log-rank test: p = .968) and no significant between-group differences in adverse events. Effect sizes at end point were medium to high for improvements in MADRS and 9 of the 12 secondary readouts. CONCLUSIONS: NAC appears a safe and effective augmentation strategy for depressive symptoms in bipolar disorder.

http://www.ncbi.nlm.nih.gov/pubmed/18534556

Biol Psychiatry. 2008 Feb 1;63(3):338-40. Epub 2007 Aug 24.

N-acetylcysteine reduces extinction responding and induces enduring reductions in cue- and heroin-induced drug-seeking.

Zhou W, Kalivas PW.

Department of Neurosciences, Medical University of South Carolina, Charleston, South Carolina 29425, USA.

BACKGROUND: Previous studies show that the acute administration of N-acetylcysteine (NAC) inhibits the desire for cocaine in addicts and cocaine-seeking in animals. METHODS: Rats were trained to self-administer heroin, and the reinstatement model of drug seeking was used to determine whether chronic NAC treatment inhibited heroin-seeking. RESULTS: Daily NAC administration inhibited cue- and heroin-induced seeking. Moreover, repeated NAC administration during extinction training reduced extinction-responding and inhibited cue- and heroin-induced reinstatement for up to 40 days after discontinuing daily NAC injection. CONCLUSIONS: These data show that daily NAC inhibits heroin-induced reinstatement and produces an enduring reduction in cue- and heroin-induced drug seeking for over 1 month after the last injection of NAC. Both the inhibitory effect of NAC on the reinstatement of heroin-seeking and the ability of NAC to reduce extinction-responding support clinical evaluation of repeated NAC administration to decrease in drug-seeking in heroin addicts.

http://www.ncbi.nlm.nih.gov/pubmed/17719565

Free full text: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2709691/?tool=pubmed

Nat Neurosci. 2003 Jul;6(7):743-9.

Neuroadaptations in cystine-glutamate exchange underlie cocaine relapse.

Baker DA, McFarland K, Lake RW, Shen H, Tang XC, Toda S, Kalivas PW.

Department of Physiology and Neuroscience, Medical University of South Carolina, Charleston, South Carolina 29425, USA.

Repeated cocaine treatment and withdrawal produces changes in brain function thought to be involved in relapse to drug use. Withdrawal from repeated cocaine reduced in vivo extracellular glutamate in the nucleus accumbens of rats by decreasing the exchange of extracellular cystine for intracellular glutamate. In vivo restoration of cystine/glutamate exchange by intracranial perfusion of cystine or systemically administered N-acetylcysteine normalized the levels of glutamate in cocaine-treated subjects. To determine if the reduction in nonvesicular glutamate release is a mediator of relapse, we examined cocaine-primed reinstatement of drug seeking after cocaine self-administration was stopped. Reinstatement was prevented by stimulating cystine/glutamate exchange with N-acetylcysteine and restoring extracellular glutamate. Thus, withdrawal from repeated cocaine increases susceptibility to relapse in part by reducing cystine/glutamate exchange, and restoring exchanger activity prevents cocaine-primed drug seeking.

http://www.ncbi.nlm.nih.gov/pubmed/12778052

Biol Psychiatry. 2007 Sep 15;62(6):652-7. Epub 2007 Apr 18.

N-acetyl cysteine, a glutamate-modulating agent, in the treatment of pathological gambling: a pilot study.

Grant JE, Kim SW, Odlaug BL.

Department of Psychiatry, University of Minnesota School of Medicine, 2450 Riverside Avenue, Minneapolis, MN 55454, USA. grant045@umn.edu

BACKGROUND: Although pathological gambling (PG) is relatively common, pharmacotherapy research for PG is limited. N-acetyl cysteine (NAC), an amino acid, seems to restore extracellular glutamate concentration in the nucleus accumbens and therefore offers promise in reducing addictive behavior. METHODS: Twenty-seven subjects (12 women) with DSM-IV PG were treated in an 8-week open-label trial of NAC with responders (defined as a > or = 30% reduction in Yale Brown Obsessive Compulsive Scale Modified for Pathological Gambling [PG-YBOCS] total score at end point) randomized to 6 weeks of double-blind NAC or placebo. RESULTS: The PG-YBOCS scores decreased from a mean of 20.3 +/- 4.1 at baseline to 11.8 +/- 9.8 at the end of the open-label phase ($p < .001$). Sixteen of 27 subjects (59.3%) met responder criteria. The mean effective dose of NAC was 1476.9 +/- 311.3 mg/day. Of 16 responders, 13 entered the double-blind phase. Of those assigned to NAC, 83.3% still met responder criteria at the end of the double-blind phase, compared with only 28.6% of those assigned to placebo. CONCLUSIONS: The efficacy of NAC lends support to the hypothesis that pharmacological manipulation of the glutamate system might target core symptoms of reward-seeking addictive behaviors such as gambling. Larger, longer, placebo-controlled double-blind studies are warranted.

http://www.ncbi.nlm.nih.gov/pubmed/17445781

CNS Spectr. 2009 Jul;14(7):357-60.

Nail-biting stuff? The effect of N-acetyl cysteine on nail-biting.

Berk M, Jeavons S, Dean OM, Dodd S, Moss K, Gama CS, Malhi GS.

Department of Clinical and Biomedical Sciences, University of Melbourne, Australia.
mikebe@barwonhealth.org.au

N-acetyl cysteine (NAC) is a widely available nutraceutical with a variety of actions. As a precursor of cysteine and glutathione, it has antioxidant properties that may impact on mood and contribute to an effect on impulsivity and obsessive behaviour. Via its additional effect on glutamate via the cystine-glutamate exchange system, NAC has been shown to mediate impulsivity in preclinical models of addiction, reduce craving, and cue extinction. Further, by boosting glutathione, NAC acts as a potent antioxidant and has been shown in two positive, large-scale randomized placebo-controlled trials to affect negative symptoms in schizophrenia and depression in bipolar disorder. We describe three cases in which its actions specifically on nail-biting and associated anxiety may offer a potential treatment. The spontaneous findings are reported as part of an ongoing treatment trial examining the utility of NAC in bipolar disorder. Its actions, if robustly replicated, also point to potential treatment targets in glutathione or glutamate pathways in the brain.

http://www.ncbi.nlm.nih.gov/pubmed/19773711

Biochem Pharmacol. 2008 Jan 1;75(1):218-65. Epub 2007 Jun 30.

Glutamatergic substrates of drug addiction and alcoholism.

Gass JT, Olive MF.

Center for Drug and Alcohol Programs, Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, SC 29425, USA.

The past two decades have witnessed a dramatic accumulation of evidence indicating that the excitatory amino acid glutamate plays an important role in drug addiction and alcoholism. The purpose of this review is to summarize findings on glutamatergic substrates of addiction, surveying data from both human and animal studies. The effects of various drugs of abuse on glutamatergic neurotransmission are discussed, as are the effects of pharmacological or genetic manipulation of various components of glutamate transmission on drug reinforcement, conditioned reward, extinction, and relapse-like behavior. In addition, glutamatergic agents that are currently in use or are undergoing testing in clinical trials for the treatment of addiction are discussed, including acamprosate, N-acetylcysteine, modafinil, topiramate, lamotrigine, gabapentin and memantine. All drugs of abuse appear to modulate glutamatergic transmission, albeit by different mechanisms, and this modulation of glutamate transmission is believed to result in long-lasting neuroplastic changes in the brain that may contribute to the perseveration of drug-seeking behavior and drug-associated memories. In general, attenuation of glutamatergic transmission reduces drug reward, reinforcement, and relapse-like behavior. On the other hand, potentiation of glutamatergic transmission appears to facilitate the extinction of drug-seeking behavior. However, attempts at identifying genetic polymorphisms in components of glutamate transmission in humans have yielded only a limited number of candidate genes that may serve as risk factors for the development of addiction. Nonetheless, manipulation of glutamatergic neurotransmission appears to be a promising avenue of research in developing improved therapeutic agents for the treatment of drug addiction and alcoholism.

http://www.ncbi.nlm.nih.gov/pubmed/17706608

Free full text: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2239014/?tool=pubmed

Environ Health Perspect. 1998 May;106(5):267-71.

N-acetylcysteine as an antidote in methylmercury poisoning.

Ballatori N, Lieberman MW, Wang W.

Department of Environmental Medicine, University of Rochester School of Medicine, NY 14642, USA.

Methylmercury is a ubiquitous environmental pollutant and potent neurotoxin. Treatment of methylmercury poisoning relies almost exclusively on the use of chelating agents to accelerate excretion of the metal. The present study demonstrates that oral administration of N-acetylcysteine (NAC), a widely available and largely nontoxic amino acid derivative, produces a profound acceleration of urinary methylmercury excretion in mice. Mice that received NAC in the drinking water (10 mg/ml) starting at 48 hr after methylmercury administration excreted from 47 to 54% of the 203Hg in urine over the subsequent 48 hr, as compared to 4-10% excretion in control animals. When NAC-containing water was given from the time of methylmercury administration, it was even more effective at enhancing urinary methylmercury excretion and at lowering tissue mercury levels. In contrast, excretion of inorganic mercury was not affected by oral NAC administration. The ability of NAC to enhance methylmercury excretion when given orally, its relatively low toxicity, and is wide availability in the clinical setting indicate that it may be an ideal therapeutic agent for use in methylmercury poisoning.

http://www.ncbi.nlm.nih.gov/pubmed/9520359

Free full text: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1533084/?tool=pubmed

Br J Pharmacol. 2000 Jul;130(6):1219-26.

Beneficial effects of n-acetylcysteine on ischaemic brain injury.

Cuzzocrea S, Mazzon E, Costantino G, Serraino I, Dugo L, Calabrò G, Cucinotta G, De Sarro A, Caputi AP.

Institute of Pharmacology, School of Medicine, University of Messina, Torre Biologica, Policlinico Universitario Via C. Valeria, Italy. salvator@imeuniv.unime.it

1. Nitric oxide (NO), peroxynitrite, formed from NO and superoxide anion, poly (ADP-ribole) synthetase have been implicated as mediators of neuronal damage following focal ischaemia. Here we have investigated the effects of n-acetylcysteine (NAC) treatment in Mongolian gerbils subjected to cerebral ischaemia. 2. Treatment of gerbils with NAC (20 mg kg(-1) 30 min before reperfusion and 1, 2 and 6 h after reperfusion) reduced the formation of post-ischaemic brain oedema, evaluated by water content. 3. NAC also attenuated the increase in the brain levels of malondialdehyde (MDA) and the increase in the hippocampus of myeloperoxidase (MPO) caused by cerebral ischaemia. 4. Positive staining for nitrotyrosine was found in the hippocampus in Mongolian gerbils subjected to cerebral ischaemia. Hippocampus tissue sections from Mongolian gerbils subjected to cerebral ischaemia also showed positive staining for poly (ADP-ribose) synthetase (PARS). The degree of staining for nitrotyrosine and for PARS were markedly reduced in tissue sections obtained from animals that received NAC. 5. NAC treatment increased survival and reduced hyperactivity linked to neurodegeneration induced by cerebral ischaemia and reperfusion. 6. Histological observations of the pyramidal layer of CA1 showed a reduction of neuronal loss in animals that received NAC. 7. These results show that NAC improves brain injury induced by transient cerebral ischaemia.

http://www.ncbi.nlm.nih.gov/pubmed/10903958

Free full text: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1572181/?tool=pubmed