Cognitive Issues and Lupus
26th Annual Maryland Lupus Summit
November 2, 2013
8160 Maple Lawn Blvd.
Suite 200
Fulton, MD 20759
(443) 212-8378
www.sarahweden.com

“...the inertia of parkinsonism, the impulsiveness of Tourette’s syndrome, the
distractibility of ADHD, the perseveration of OCD, the lack of empathy or “theory of
mind” in autism or chronic schizophrenia, can all be understood, in large part,
Goldberg feels, as due to the resonances, the secondary disturbances, in the function
of the frontal lobes.”
- Oliver Sacks

History of Cognitive
e Dysfunction in SLE

First mentioned in 1875 by Moritz Kaposi
Sir William Osler described patients with CNS lupus
over 100 years ago
First formal SLE study 1945
50’s - 60’s neuropsychiatric SLE (NPSLE)
associated with CNS vasculitis

History of Cognitive
e Dysfunction in SLE

1968: Mass General Hospital study: CNS vasculitis rare
1980’s: antiphospholipids antibody (anticaardiolipn)
introduced
Cognitive dysfunction described as a syndrome
1999: American College of Rheumatology: 19 syndromes
19 Neuropsychiatric Syndromes: Central Nervous System

- Aseptic meningitis
- Cardiovascular disease
- Demyelinating syndrome
- Headache
- Movement disorder
- Myelopathy
- Seizure disorder
- Acute confusional state

19 NPSLE Syndromes: Peripheral Nervous System

- Guillain–Barre’ syndrome
- Autonomic disorder
- Mononeuropathy
- Cranial neuropathy
- Myasthenia-like syndrome
- Plexopathy
- Peripheral neuropathy

American College of Rheumatology Research Committee, 1999

Cognitive Dysfunction or Cognitive Impairment aka “Lupus fog”

Most common manifestation

The prevalence of cognitive impairment in SLE ranges from 15-60%

Fluctuating and transient pattern to cognitive dysfunction in SLE
Little known about role of brain development and cognition in pediatric SLE

Cognitive impairment ranges from concentration difficulties & decrease in school performance to frank confusion and coma

Occurs in 20% to 57% of children with NP-SLE

Antiphospholipid Antibodies (APL)

Induce a procoagulant state & associated with focal manifestations of NPSLE (e.g., stroke and seizures)

Persistently elevated levels of anticardiolipin antibodies associated with decline in cognitive functioning possibly because of tiny clots within blood vessels

- Kozora et al., 2008

Advances in neuroscience allowed greater understanding of cognitive impairment in lupus

Possible Underlying Mechanisms Cognitive Dysfunction in SLE

Antiphospholipid Antibodies (APL)

Cytokines

Mediators of inflammation

One study identified a relationship with learning deficits in SLE patients

Another study showed relation between elevated levels of C-reactive protein, a nonspecific marker of inflammation & deficits in information processing

- Kozora et al., 2008
Possible Underlying Mechanisms Cognitive Dysfunction in SLE

**Vascular Abnormalities**
Evidence post-mortem of diffuse, noninflammatory microvascular abnormalities

Changes appear independent of aPL, are found in proximity to cerebral microinfarction, & suggest causal relationship possibly associated with cognitive dysfunction in SLE

- Kozora et al., 2008

Possible Underlying Mechanisms Cognitive Dysfunction in SLE

**Matrix Metalloproteinases**
In patients with NPSLE, especially those with cognitive impairment, levels of MMP-9 are elevated in serum & CSF

Correlation btw CSF MMP-9 levels, proinflammatory cytokines, & biomarkers of neuronal & glial degradation in SLE patients suggests enhanced production of MMP-9 linked to CNS damage in SLE

- Kozora et al., 2008

Possible Underlying Mechanisms Cognitive Dysfunction in SLE

**Neuropeptides**
Neuropeptides linked to behavioral & cognitive changes in animal & human studies

Increased serum levels of vasopressin & calcitonin gene-related peptide observed in persons with SLE cognitive dysfunction

- Kozora et al., 2008

Mood and Cognition

**Depression**

“...not being able to initiate, not being able to think clearly, not being able to care about your family – those are secondary to something your attention is directed to internally but that is a false signal.”

- Helen Maybery, MD; Emory U
Mood and Cognition

Mood disorder (depression/anxiety), fatigue & pain highly associated with cognitive dysfunction
Fatigue may result from depression and/or disease activity
Cytokines may play a role in fatigue

Deficits in executive control & inhibition related to sustained processing of negative material & rumination may maintain low mood & hinder recovery from negative emotional state

Aggravating Factor in SLE Cognitive Dysfunction

Depression = “Brain-lock” – Ratey, 2008
Depression & anxiety ‘freeze up’ same brain areas implicated in lupus cognitive dysfunction
PFC (frontal lobe) goes “offline.” frozen, no longer accessing executive functions to tackle problems efficiently giving rise to sense of Lupus Fog

“Offline” in SLE cognitive dysfuntion, maybe more with added mood issues

Positron emission tomography (PET) of 12 with SLE: hypometabolism in frontal lobe area
PET of non-SLE persons with depression also show hypometabolism in frontal lobe area
White matter hyperintensities seen in MRI findings in depression
Neuroimaging findings

White matter hyperintensities most common MRI finding in SLE cognitive impairment

Normal findings on MRI showed abnormal findings in the frontal white matter and the corpus callosum areas with use of DTI.

Pediatric onset SLE study: greater activation in frontoparietal areas than in controls, same cognitive operations required more cortical activity suggesting underlying white matter damage

Abnormal fMRI activity in SLE patients, suggesting "white matter connectivity" disruption, resulting in "neuronal network dysfunction"

- Kozora et al., 2008

Executive Functions

2013 Kozora et al. study:

"...early white matter damage interferes with working memory in SLE and provides further insight into the neurobiological basis of mild cognitive dysfunction related to microstructural white matter injury."

Executive functions deficits may be the prominent cognitive characteristic associated with white matter pathology.
Volitional control implies the ability to anticipate the consequences of one’s action, the ability to decide whether the action should be taken, and the ability to choose between action and inaction.

The capacity for volitional control over one’s actions is important, perhaps central ingredient of social maturity. The capacity for volitional behavior depends on the functional integrity of the frontal lobes.

- Elkhonon Goldberg, 2001

Prefrontal lobe highly involved in 2 related but different EF abilities:

1. Dorsolateral prefrontal areas:
   Mediates and associated with classic executive functions:
   Complex problem solving, decision making, verbal fluency, & working memory
   Specifically allows the organization of information to facilitate a response

- Bonelli & Cummings, 2007

Orbitofrontal and medial (anterior cingulate) prefrontal circuits:
“Emotional/motivational executive functions:”
Coordinating cognition & emotion/motivation regulation of one’s own social behavior & decision-making involving emotional & personal interpretation.

- Ardila, 2008

Frontal regions (COLD/TOP): working memory, attention controls, planning, learning, and emotional regulation
Subcortical structures (HOT/DOWN): regulating higher "top" processes that control cognition
A series of parallel, segregated frontal-subcortical circuits constituting an important effector mechanism that allows the organism to interact adaptively with its environment.

- Bonelli & Cummings, 2007
Executive Functions & SLE Cognitive Impairment

Studies have shown that impairments in either the "cold" or "hot" component of executive functions may have devastating effects on people’s everyday life activities, including the ability to work and attend school, function independently at home, or develop and maintain appropriate social relations.

- Chan et al, 2008

Neuropsychological Findings

ACR Research Committee:

Cognitive Dysfunction:

“…significant deficits in any or all of the following cognitive functions: complex attention, executive skills (e.g., planning, organizing, sequencing), memory (e.g., learning, recall), visual-spatial processing, language (e.g., verbal fluency), and psychomotor speed.”
What NP Testing actually shows:

Kozora et al, 2013:

Paced Auditory Serial Addition Test (PASAT), a measure of working memory, to 73 patients with SLE

29% impaired working memory on the PASAT

Lower total PASAT score correlated with higher left frontal microstructural white matter damage

ACR-SLE Battery:

- The Revised Wechsler Adult Intelligence Scale (WAIS-R) Digit Symbol Substitution Test (Digit Symbol)
- The Trail Making Test part B (Trail Making-B)
- The Stroop Color and Word Test (Stroop Color-Word)
- California Verbal Learning Test (CVLT)
- Rey-Osterrieth Complex Figure Test
- The Wechsler Adult Intelligence Scale - III Letter Number Sequencing
- The Controlled Oral Word Association Test (letter fluency) and the Animal Naming Test (category fluency)
- The Finger Tapping Test

Lupus Fog

Memory

- Difficulty recalling conversations, tasks, or appointments
- Misplacement of items of importance like keys, phone, bills etc.
- Forgetting conversations
- An inability to process "new" information and learn it
- Difficulty in completing familiar tasks like remembering dates/important appointments, balancing a checkbook or dialing a familiar number
- Friends, family, and co-workers frustrated, not always "getting it"

EF Deficits and Lupus Fog

Concentration

- Difficulty following directions
- Trouble remembering recent events
- Reading the same sentence over & over
- Trouble learning new tasks or absorbing information
- Problems multi-tasking
EF Deficits and Lupus Fog

**Thinking skills**

- Problems registering and understand the information
- Difficulty coming up with solutions, planning, organizing, and thinking critically
- At a loss for words
- Overwhelmed in situations you weren’t before: deer in headlights

Lupus fog is a result of many factors including the disease itself, related cognitive dysfunction, and often aggravating depression, anxiety, fatigue, and/or pain

**Executive Functions**

**DEFINING EXECUTIVE FUNCTIONS**

McCloskey’s Model of EF

**Self-Control**

- SELF ACTIVATION
- SELF REGULATION
- Attention
- Intention
- Evaluation
- Solution
- Execution
- Recollection

**Metacognition**

- SELF REALIZATION
- SELF DETERMINATION
- SELF-GENERATION
- TRANS-SELF
- INTEGRATION
Treatment of Cognitive Dysfunction in SLE

The initial strategy for management of cognitive dysfunction in patients with SLE: identify & treat secondary or exacerbating causes of dysfunction.

Limited studies of NPSLE patients requires pulling from experiences of other diseases for treatment rationale.

Treatment: Medication

Pharmacologic therapy for SLE-cognitive dysfunction

- Improvement in 5 of 8 patients completing trial of daily treatment 0.5 mg/kg prednisone. - Denberg et al., 1994

- Longitudinal observational study: regular aspirin use in SLE patients associated with better cognitive performance than those not taking aspirin. - McLaughlin et al., 2006.

- Pharmacologic treatment aimed at “cognitive enhancement” has not yet been studied in SLE cognitive impairment.

Cognitive Behavior Therapy

Depression: impaired frontal-subcortical functioning in the onset and maintenance of depressive symptoms

- CBT works from PFC downwards to modify thoughts so that we can challenge sense of helplessness. - Ratey, 2008
**Behavioral Therapy**

**Behavioral activation:**
MDD characterized by anomalous neurobiological responses to pleasant stimuli, a pattern that may be linked to symptoms of anhedonia.

MDD display striatal dysfunction during anticipatory phase.

Decreased reward seeking behaviors & functioning of the striatum.

BATD: exposure to reinforcing situations & inhibiting behavioral withdrawal characteristic of MDD encouraged - Dichter et al, 2009

Down-up chain of events

---

**The Effects of Psychotherapy on Neural Responses to Rewards in Major Depression**

Gabriel S. Dichter, Jennifer N. Felder, Christopher Potty, Joshua Bazell, Monique Ernst, and Marcia J. Smawak

**Background:** Unipolar major depressive disorder (MDD) is characterized by anomalous neurobiological responses to pleasant stimuli, a pattern that may be linked to symptoms of anhedonia. However, the potential for psychotherapy to normalize neurobiological responses to pleasant stimuli has not been evaluated.

**Methods:** Twelve adults with and 12 adults without MDD participated in two identical functional magnetic resonance imaging scans that used a Wheel of Fortune task. Between scans, MDD participants received Behavioral Activation Therapy for Depression, a psychotherapy modality designed to increase engagement with rewarding stimuli and reduce avoidance behaviors.

**Results:** Seventy-five percent of adults with MDD were treatment responders, achieving post-treatment Hamilton Rating Scale for Depression scores of 6 or below. Relative to changes in base function in the matched nondepressed group, psychotherapy resulted in functional changes in structures that mediate responses to rewards, including the prefrontal cortex and the right insula. These changes were associated with increased neural response to rewarding stimuli during reward feedback.

**Conclusions:** Behavioral Activation Therapy for Depression, a psychotherapy modality designed to increase engagement with rewarding stimuli and reduce avoidance behaviors, results in improved functioning of unique reward structures during different temporal phases of reward processing, including the neural substrate of reward anticipation.

---

**Behavioral Therapy**

General principles in Treatment of Anxiety & Depression

Essentials for recovery from depression include:

- Engagement in rewarding activities
- Pleasure
- Mastery
- Exercise
- Novelty
- Social

To effectively manage anxiety, essentials for recovery include:

- Facing fears/discomfort
- Relinquishing escape/avoidance behaviors

---

**CBT in Lupus**

Restructuring of illness beliefs and cognitions

Relationship btw illnesses, mood, & behavior in chronic illnesses

Individuals regulate their health-related behaviors according to the beliefs they hold in regard to the specific components of their illness representations - Goodman et al, 2005
CBT

Individuals organize their experience around 5 components:

- **Identity**: label person uses to described illness & symptoms
- **Cause**: personal ideas about cause of illness
- **Consequences**: expected short & long term outcomes of illness
- **Timeline**: how long one believes illness will last
- **Cure or control**: Person’s ideas about what s/he or healthcare providers can do to influence course of illness

- Goodman et al, 2005

Elements of CBT intervention

**Cognitive Aspect:**

- Understanding role of mood/anxiety in chronic illness
- Psychoeducation
- ID, recording, and challenging negative automatic thoughts & cognitive errors
- Cognitive restructuring
- Symptom-management: relaxation exercises, exercises, distractions, guided imagery
- Assertiveness training
- Social skills training

- Goodman et al, 2005

Elements of CBT intervention

**Behavioral aspect:**

- Behavioral experiments
- PMR
- Goal setting
- Action plans

- Goodman et al, 2005
CBT in Lupus

Anxiety/depression levels much lower than at start and below population average – maintained.

Could make coping with the disease easier

Experienced fewer physical and emotional problems in their daily lives

Mindfulness Meditation

“A collection of meditation practices designed to enhance the ability to remain immersed nonjudgmentally in the present moment” (Kabat-Zinn, 2003)

Elements involve focused attention and breathing

Mindful – increasing ability to focus & direct attention thereby changing information processing patterns associated with emotional difficulties

2 aspects of cognitive operations likely affected: Attention regulation (self control) and a “nonstriving” or accepting attitude (metacognitive)

– Hamilton et al, 2006

Mindfulness Meditation

Buddhist teaching: Suffering comes from attachment to transient states including health and life.

Kabat-Zinn:

Rejecting stress like “Sailing straight into wind”... “If you only know how to sail with the wind at your back, you will only go where the wind blows you”

Emphasizes tuning in to one’s inner resources and responses, which can help “ground” ourselves in such a way that we can use the pressure of the problem itself to propel us through it

Attending to the source of discomfort, patients may find that they are in less pain than thought originally.

– Hamilton et al, 2006

Mindfulness

MBSR at U Mass: reduction in stress regardless of cause

Meta-analysis showed effectiveness of mindfulness - Baer, 2003

Soldiers with mindfulness instruction undergoing training stress preserved working memory while soldiers without experienced a depletion in working memory.

– Zylowska, 2012
Mindfulness

UCLA study focused on executive function skill building in 2nd/3rd grades with mindfulness training in school:

Children with poor executive functions had significant gains in EF skills after 8-week mindfulness training.

– Zylowska, 2012

Mindfulness

Mindfulness 2010 review of 23 controlled studies:
Early phases of mindfulness training associated with improvement in selective & executive attention whereas later phases bring improvement in alert, sustained attention.

– Zylowska, 2012

Mindfulness Meditation in SLE

“The ability to remain focused on daily goals despite pain or other unpleasant physical probably crucial for maintaining normal level of functioning for those with chronic illnesses....

Attention regulation skills may be crucial for optimal ability to exercise control over attention may be even more critical for those vulnerable to affective dysregulation as in chronic illnesses.”

– Hamilton et al., 2006

Mindfulness Meditation

In chronic illness like SLE:
May change illness perceptions
May reduce pain symptoms
Mindfulness meditation enhances emotional regulatory skills
Associated with changes in metacognitive/PFC/EF processes as they relate to mood.
Plausible that interventions strengthening attentional control may produce observable change in frontal lobe/executive functioning

– Hamilton et al., 2006
Mindfulness Meditation

Daily meditation practice necessary to master attention regulatory skill such as attention focusing and shifting

Requires time commitment

– Hamilton et al, 2006

Cognitive Rehabilitation Therapy

Aids individual in developing skills & learning compensatory strategies to improve functioning at home, school, & work.

Addresses difficulties with attention, learning new information, memory, time management, planning, organization, and problem-solving

Focused on enhancing metacognition - "remembering to remember": Top-down chain of events.

Cognitive Rehabilitation Therapy

Evidence to support interventions for attention, memory, social communication skills, executive function, & for comprehensive-holistic neuropsychologic rehabilitation after TBI

- Cicerone et al., 2011

Results of a pilot study of 17 women with SLE suggest that meta-memory and memory self-efficacy improve after participation

- Harrison, et al., 2005

Memory Strategy
Memory Strategy

How does it work?

Memory enhanced when cognitive processes engaged during learning match those for subsequent retrieval.

Requires person to perform same cognitive process during learning phase as during delayed recall phase.

Same neural circuits accessed repeatedly with quizzing.

Cognitive Rehabilitation Therapy

Quiz self or have others quiz you on to-be-learned material.

Can support daily living skills (eg. errands).

Can help better with learning demands of work & school.

Retrieval practice - easy to use.

Cognitive Rehabilitation Therapy

Johnstone & Stonnington, 2009:

General memory tips

Work in environment in which distractions are minimized (you may considering using ear plugs while concentrating on a task, working facing a wall rather than a window, or clearing a desk before beginning work).

1 thing at a time. Before changing tasks, write down specifically what you are doing to avoid duplicating or omitting steps when the task is resumed.

Talking to yourself through a task (self-coaching) may help maintain focus in what you are doing.

Introduce new information only after previously presented information has been learned.

Make it personal - helps connect with previously learned information.

Repetition of information helps.

Cognitive Rehabilitation Therapy

Johnstone & Stonnington, 2009:

Memory:

Post-it notes in conspicuous places.

Break information down into smaller chunks.

Tape record new information and replay messages frequently. Use available apps etc. to help organize, remember, and remind you.
**General tips to improve alertness/attention levels**

Activity pacing (breaks, naps, rests). Schedule & take frequent breaks during the day to mitigate fatigue, a contributor to inattention.

Frequent breaks will help minimize fatigue & improve stamina.

Scheduling tasks with higher arousal demands when most alert

Work on least interesting material when most alert

---

**For initiation problems**

Use environmental cues and triggers such as alarms, visual signs, written notes or calendars

Link behaviors that occur together naturally (e.g., meds at mealtimes)

---

**Disorders of self-regulation:**

Mnemonic strategies such as Plan, Do, Check/Study, Act (PDCA) cycle

Use of apps/electronics to assist with organization and memory

Environmental modifications

---

**General strategies to improve executive functioning skills:**

- Practice of repetition (practice makes perfect)
- Progress along a hierarchy of tasks from basic to complex
- Consistently check work carefully
- Identify and use strengths to compensate for impairments
- Make daily activities as routine as possible (lunch at 12 noon, Tuesday is grocery day)
- Pace yourself: don’t overdo it by taking on more that you are capable – know your limits.
- Allow extra time to complete tasks
- Organize tasks so that materials needed to perform a task are close by and in order needed to perform the task

---

**Biofeedback**

**Effects of a Stress-Reduction Program on Psychological Function, Pain, and Physical Function of Systemic Lupus Erythematosus Patients: A Randomized Controlled Trial**

**Objective:** To assess the effects of a stress-reduction program on psychological function, and perceived health, in women with systemic lupus erythematosus, a chronic inflammatory autoimmune disease. A randomized, controlled trial was conducted with 24 women, in two groups: stress-reduction program (12 women) and control (12 women). Results: The stress-reduction program group showed significant improvement in psychological function, compared to the control group. Conclusion: Stress-reduction programs may be effective in improving the psychological function of women with systemic lupus erythematosus. **ACT WORKS:** Cognitive, Behavior, and Mindfulness-based therapies.
Exercise

Individuals with SLE have diminished aerobic capacity that their ability to perform daily domestic activities & occupational activities & recreational pursuits are seriously hampered. – Goodman et al 2005

American College of Rheumatology: Individuals with lupus can exercise (e.g., flexibility & strengthening exercises, low impact aerobic activity)

Exercise: Attention

Improves Attention:

Boosts DA and NE

Improvement in cortex’s “signal to noise ratio”

– Spark, Ratey, 2008
Exercise: Learning

- Improves alertness, attention, and motivation
- Prepares & encourages nerve cells to bind to one another (cellular basis for logging in new information)
- Improves plasticity in the hippocampus by spurring development of new nerve cells from stem cells in hippocampus
- Exercise elevates neurotransmitters, creates new blood vessels that pipe in growth factors, & spawns new cells
- One study showed 30min exercise 2-3x/week improved EF (involving coordinating activity)

Exercise: Mood

- Exercise: both top-down and down-up energizing effect enhancing energy, interest, and motivation, & lessening fatigue
- From PFC, adjusts chemicals including DA, 5HT, and NE resulting in changed self concept
- Frees up PFC so we can reorient to good things & validates that we can create change & self-intiate, increasing sense of mastery & accomplishment

   – Spark, Ratey, 2008

Exercise: Anxiety

- “By activating the SNS thru exercise, you break free from the trap of passively waiting and worrying, and thus prevent the amygdala from running wild and reinforcing the danger-filled view life is presenting. Instead when you respond with action, you send information down a different pathway of the amygdala, paving a safe detour and wearing in a good groove. You’re improving alternate connections, actively learning an alternate reality.” – Ratey, 2008

Exercise: Protective factor

- Neurotropic factor BDNF protects neurons against cortisol in areas that control mood, including the hippocampus
- BDNF “fertilizer that encourages neurons to connect to one another & grow (vital component of neuroplasticity and neurogenesis)
- High levels of cortisol (stress) can decrease BDNF, exercise does the opposite
- Exercise boosts BDNF at least as much as meds
**CAMs**

**NCCAM:**

“A group of diverse medicinal and health care systems, practices, and products that are not presently considered to be part of conventional medicine”

Holistic approach treating whole body

Biggest problem: not enough research

---

**Effects of Supervised Cardiovascular Training Program on Exercise Tolerance, Aerobic Capacity, and Quality of Life in Patients With Systemic Lupus Erythematosus**

**Objective:** To determine if supervised cardiovascular training improves exercise tolerance, aerobic capacity, depression, functional capacity, and quality of life in patients with systemic lupus erythematosus (SLE).

**Methods:** Daily women with SLE (n=16) were evaluated weekly. Markers of the visual analog scale for pain, scale for fatigue, Beck Depression Inventory, and Health Assessment Questionnaire (HAQ) were measured. The training protocol included aerobic exercise, strength, and flexibility training for 16 weeks. The intervention group was compared to a control group with no intervention.

**Results:** The intervention group showed significant improvements in exercise tolerance, aerobic capacity, and quality of life compared to the control group.

**Conclusions:** This study showed significant improvements in exercise tolerance, aerobic capacity, quality of life, and depression after a supervised cardiovascular training program in patients with SLE.

---

**TCM:** acupuncture and acupressure (to stimulate vital flow and dissolve blockages along channels, herbs, diet changes)

Homoeopathy: use of small doses of substances to stimulate healing

Mind-Body therapies: Yoga, tai chi, qi qong

Works to increase ability of mind on physical health & enhance communication btw mind & body
What do a violinist, New York cabbie, dyslexic child and stroke patient have in common?

**NEUROPLASTICITY**

“The pattern of activity of neurons in sensory areas can be altered by patterns of attention....Experience coupled with attention leads to physical changes in the structure and future functioning of the nervous system.” – Merzenich, 1996

“Attention is a key factor in neuroplasticity. Where we direct our attention determines which neural circuits become engaged and modified.” – Zylowska, 2012

Neuroplasticity

By consciously and repeatedly activating our brains in certain ways (via practice through intervention), we can potentially affect and structure our brains.

Further reinforcing/strengthening alternate neural grooves, changing experiences, opportunities, and quality of life.

**Polytherapy, such as:**

- Behavioral activation strategies: down-up
- Metacognitive strategies: top-down
- Exercise: top-down/down-up
- Mindfulness: top-down/down-up

“Knowledge, in general, and neurobiological knowledge in particular have a role to play in human destiny.”

- Antonio Damasio, Descartes Error