

SiNAPSA Neuroscience Conference 2013

27-29 September 2013

Faculty of Medicine, Ljubljana, Slovenia

Plenary lectures and special talks



Integrating network structure and function in the human brain

Olaf Sporns

Department of Psychological and Brain Sciences, Indiana University, USA

Recent advances in network science have greatly increased our understanding of the structure and function of many networked systems, ranging from transportation networks, to social networks, the internet, ecosystems, and biochemical and gene transcription pathways. Network approaches are also increasingly applied to the brain, at several levels of scale from cells to entire brain systems. This lecture will focus on network approaches to understanding the large-scale connectivity of the human brain, the “human connectome”. Early studies in this field have focused on mapping brain network topology and identifying some of its characteristic features, including small world attributes, modularity and hubs. More recently, the emphasis has shifted towards linking brain network topology to brain dynamics, the patterns of functional interactions that unfold during both rest and task conditions. In my talk I will give an overview of recent work characterizing the structure of complex brain networks, with particular emphasis on studies demonstrating how the brain’s structural topology constrains and shapes its capacity to process and integrate information.



Engineering therapies for neurodegenerative disease: ALS, Huntington's and beyond

Don W. Cleveland

The Ludwig Institute and Department of Cellular and Molecular Medicine,
University of California at San Diego, USA

The genes whose mutation is now known to cause the major neurodegenerative diseases are widely expressed, including superoxide dismutase (SOD1) whose mutation causes an inherited form of the fatal, adult motor neuron disease ALS. Mutation in SOD1 mutant causes ALS through an acquired toxicity unrelated to dismutase activity. Use of cell type-selective mutant gene silencing has demonstrated that toxicity requires mutant damage within both motor neurons and their neighbors, with mutant SOD1 within motor neurons and oligodendrocytes driving disease onset, while damage within neighboring astrocytes and microglia accelerates disease progression. Slowed disease progression has been achieved by a clinically feasible infusion of DNA antisense oligonucleotides (ASOs) that direct destruction of SOD1 mRNA widely within the non-human primate nervous system. Additionally, disease progression can be slowed in a clinical feasible approach by reducing mutant SOD1 expression within astrocytes with a single peripheral administration of a replication defective viral delivery vector (AAV9) encoding an shRNA to target SOD1 mRNA destruction.

The landscape of disease mechanism in ALS was reset with discovery that the largest genetic cause of ALS is dominant, hexanucleotide expansion within intron 1 of the C9orf72 gene. Hexanucleotide-containing RNA foci that may sequester one or more RNA binding proteins are shown to accumulate intranuclearly in multiple cell types inside and outside of the nervous system. Proof of principle for therapy development has been achieved by identification of antisense oligonucleotides complementary to the C9orf72 pre-mRNA that selectively target degradation of C9orf72 RNAs containing the expansion.

Finally, ASO infusion to target catalytic degradation of specific mRNAs may prove to be a broadly applicable therapeutic approach. Indeed, polyglutamine expansion in the widely expressed huntingtin protein is the sole cause of Huntington's disease (HD). Infusion of ASOs targeting huntingtin mRNA effectively lowers huntingtin levels in the primary brain regions affected in HD. Transient infusion of ASOs not delays disease progression, but mediates a sustained reversal of disease phenotype that persists for much longer than the huntingtin reduction, findings that establish a feasible therapeutic strategy for sustained HD disease reversal from a "Huntingtin holiday" produced by transient therapy.



From infection hypothesis of schizophrenia to brain imaging: all make sense now?

Jiří Horáček

Prague Psychiatric Center and Third Faculty of Medicine, Charles University,
Prague, Czech Republic

Evidence from both animal and human studies implicates the essential role of immune system in the pathophysiology of a number of neuropsychiatric disorders with known or suspected developmental origins, including schizophrenia. Our previous results showed significantly increased plasma levels of IL-6, IL-10 and TNF-alpha level in first episode schizophrenia patients. These immunological mechanisms would mediate the relationship between genetic vulnerability and environmental factors. Both perinatal and postnatal candidate infections appear to be associated with the immunological dysbalance and an elevated risk of schizophrenia.

An emerging literature from epidemiologic, clinical, and preclinical studies has provided evidence that perinatal exposure to infection contributes to the etiology of these disorders. The postnatal infection of latent toxoplasmosis is associated with an increased incidence of schizophrenia with an odds ratio of 2.73, and 2.54 for first episode patients.

To address the question of interaction between genetic vulnerability and immunological dysbalance with infection etiology we studied the influence of seropositivity for latent toxoplasmosis on brain morphometry in schizophrenia patients investigated by magnetic resonance imaging. An optimized voxel-based morphometry of magnetic resonance imaging was analyzed by analysis of variance with diagnosis and seropositivity as factors. Grey matter (GM) volume was reduced in schizophrenia patients compared with controls in the cortical regions, hippocampus and in the caudate. In the schizophrenia sample we found a significant reduction of GM volume in *T. gondii* positive comparing with *T. gondii*-negative patients bilaterally in the caudate, median cingulate, thalamus and occipital cortex and in the left cerebellar hemispheres. *T. gondii*-positive and -negative controls did not differ in any cluster. Among participants seropositive to *T. gondii* the reduction of GM in the schizophrenia subjects was located in the same regions when comparing the entire sample ($p < 0.05$, FWE corrected).

Our study is the first to document that latent toxoplasmosis is connected with the reduction of GM in schizophrenia. *T. gondii* can affect gray matter by several mechanisms including kynurenine metabolites and dopamine overactivity.



Developmental dynamics of radial vulnerability of the cerebral compartments in preterm infants and neonates

Ivica Kostović

Croatian Institute for Brain Research, Zagreb, Croatia

Neurogenetic events (proliferation, migration, axonal growth, dendritic differentiation, synaptogenesis etc.) in the fetal cerebrum take place in transient, cytoarchitectonically defined, laminar compartments which are stratified along radial axis of the cerebral wall (ventricle-pia). Neuroimaging techniques offer opportunity to visualize transient compartments in vivo and track their dynamic reorganization during perinatal period. In order to explain radial vulnerability we shall discuss: 1. the nature of neurogenetic processes within the given compartments, 2. radial extent of lesion, 3. complexity of cellular targets (neurons and dendrites, glia, progenitor cells, growing axons, extracellular matrix-ECM and 4. developmental “windows” of vulnerability. Growing evidence indicates that cellular elements, namely growing axons and subplate neurons and ECM determine radial vulnerability of the preterm cerebral wall. In early preterm (up to 28 postconceptual week – PCW) hypoxic-ischaemic lesions predominantly damage periventricular fibres (callosum and crossroads of pathways), subplate neurons and ECM. After 28 PCW the vulnerable are long corticocortical pathways at the interface between sagittal strata and subplate. In the newborn, radial vulnerability shifts towards gyral white matter, subplate remnant and neurons-dendrites of the cortical plate. In conclusion, developmental vulnerability changes along radial axis in relation to growing axonal strata and deep to superficial differentiation of neurons in subplate and cortical plate. These spatial and temporal patterns of vulnerability will determine cognitive, neurological and behavioural impairments after perinatal lesions. The most important translational result of our concept is that MR properties at borders between different compartments of the cerebral wall may have prognostic significance for outcome after perinatal lesion.



The motor and non-motor functions of the basal ganglia: evidence from studies of Parkinson's disease

Marjan Jahanshahi

UCL Institute of Neurology, The National Hospital for Neurology and Neurosurgery,
London, UK

Traditionally, the basal ganglia were considered purely motor structures. However, in recognition of the fact that the greatest connectivity of the basal ganglia is with the non-motor areas of the frontal cortex such as the dorsolateral prefrontal cortex, the anterior cingulate and the orbitofrontal cortex, there has been increasing appreciation of the role of these subcortical structures in non-motor associative and limbic functions. Furthermore, accidental lesions of the basal ganglia in man are most frequently associated with non-motor behavioural symptoms such as abulia and apathy. In Parkinson's disease, the most typical movement disorder associated with basal ganglia dysfunction, motor symptoms such as bradykinesia (slowness of movement), akinesia (poverty of action), tremor and rigidity as well as non-motor symptoms such as executive dysfunction and cognitive decline, depression, anxiety and apathy are amongst the core features of the illness.

In this talk, I will first illustrate involvement of the basal ganglia in several key motor functions namely, selection and inhibition, timing, and procedural learning with examples of our research findings in patients with Parkinson's disease. Second, I will provide examples of the role of the basal ganglia in non-motor functions such as cognition and learning from research results showing deficits on cognitive tasks that involve executive processing or probabilistic incremental learning in Parkinson's disease, and also consider the effects of levodopa medication or deep brain stimulation of the subthalamic nucleus on these tasks. Finally, I will discuss limbic-motor interactions that mediate motivational modulation of movement speed in Parkinson's disease and will present data showing that prospect of monetary reward, avoidance of aversive stimuli, or provision of external stimuli all influence speed of movement initiation and execution in this disorder. This evidence establishes the role of the basal ganglia and their frontal connections in a host of motor, cognitive and limbic functions.



How placebos, words and rituals change the patient's brain

Fabrizio Benedetti

Department of Neuroscience, University of Turin Medical School,
and National Institute of Neuroscience, Turin, Italy

Although placebos have long been considered a nuisance in clinical research, today they represent an active and productive field of research and, because of the involvement of many mechanisms, the study of the placebo effect can actually be viewed as a melting pot of concepts and ideas for neuroscience. Indeed, there exists not a single but many placebo effects, with different mechanisms and in different systems, medical conditions, and therapeutic interventions. For example, brain mechanisms of expectation, anxiety, and reward are all involved, as well as a variety of learning phenomena, such as Pavlovian conditioning, cognitive and social learning. There is also some experimental evidence of different genetic variants in placebo responsiveness. The most productive models to better understand the neurobiology of the placebo effect are pain and Parkinson's disease. In these medical conditions, the neural networks that are involved have been identified: that is, opioid, cannabinoid, cholecystokinin, dopamine modulatory networks in pain and part of the basal ganglia circuitry in Parkinson's disease. Important clinical implications emerge from these recent advances in placebo research. First, as the placebo effect is basically a psychosocial context effect, these data indicate that different social stimuli, such as words and therapeutic rituals, may change the chemistry and circuitry of the patient's brain. Second, the mechanisms that are activated by placebos are the same as those activated by drugs, which suggests a cognitive/affective interference with drug action. Third, if prefrontal functioning is impaired, placebo responses are reduced or totally lacking, as occurs in dementia of the Alzheimer's type.

Educational Workshop on Placebo Effect



Placebo response is often defined as an improvement in a subject's state and function, brought about by an inherently inert substance or intervention, purposefully used to elicit such a response through deceit. However, when so defined, the response to placebo inevitably yields a large explanatory gap and an even larger ethical dilemma.

Over the last two decades new research approaches have contributed significantly to a better understanding of the mechanisms underlying the placebo response. The aim of the Educational Workshop is to present and discuss some of the recent findings that allow us to redefine and reappraise the response to placebo. This new understanding of the response to placebo may lead to better designs of new treatment studies as well as to added therapeutic benefit in clinical practice, thus possibly resolving both the explanatory gap and the ethical dilemma.

Programme of the Educational Workshop

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| 8:30 - 10:30 | Session I INTRODUCTION TO THE PLACEBO EFFECT
Maja Bresjanac: Definition, research methods, and overview of the workshop
Fabrizio Benedetti: General mechanisms across (patho)physiological conditions |
| 14:30 - 16:30 | Session II MECHANISMS IN SPECIFIC CONDITIONS
Elisa Carlino: Pain
Elisa Frisaldi: Parkinson's disease
Bettina Doering: Depression
Antonella Pollo: Physical performance |
| 17:00 - 19:00 | Session III CLINICAL AND ETHICAL IMPLICATIONS
Paul Enck: Use of placebo in clinical trials
Zvezdan Pirtosek: Use of placebo in clinical practice
Jože Trontelj: Ethical guidelines on the use of placebo in clinical research and practice |
| 19:00 - 20:30 | Neuroscience and Society Event
Ethical challenges in exploring and exploiting the response to placebo |