Hyper-activation of the Rho-GTPase Rac1 via disruption of ArhGAP15 results in reduced architectural and functional complexity

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An integrative nuclear signaling module for neuronal development and regenerative medicine

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Ontogeny requires the coordinated regulation of multi-gene programs by a plethora of extracellular and intracellular signals. As a result, stem cells transition between states of self-renewal, proliferative expansion and differentiation. Disruption of this regulation may cause oncogenic transformation in which stem cells are "arrested" in the proliferative state. Systems biology postulates computational modules which integrate environmental (extra- and intra-cellular) information to control entry into the cell cycle and promote perpetual self-renewal by the stem cells. We have identified an analogous Feed-Forward-And Gate network module that effects postmitotic development and neuronal differentiation by the stem cells. In the center of this module resides a novel gene-activating mechanism "Integrative Nuclear Fibroblast Growth Factor Receptor-1 (FGFR1) Signaling" (INFS). We will discuss how stochastic molecular collisions among nuclear proteins lead to an activation of coordinate gene programs. New mechanisms are revealed by Chromatin Immunoprecipitation-sequencing (ChIP-seq) and RNA-seq, that enable neuronal development of multi- and pluri-potent stem cells. New technologies have been developed allowing to control INFS in the brain stem cells in vivo and reconstitute developmental-like neuronogenesis in the adult brain (supported by NYSTEM GRANTS C026415 and C026714, and Patrick P. Lee Foundation).

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Statistical processing of Parkinson and other movement disorders examination using multi-channel ENMG system

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The aim-of-present experimental investigation is to attempt to differentiate between those with concordant (C) and discordant (D) mirror-movements (MMs)/Mirror-Dystonia in Parkinson disease and other movement disorders writer's cramp (WC), in order to establish that there is a quantifiable difference between these two groups and to design/fabricate a multi-channel ENMG system.

12 consecutive-subjects (M:F = 11:1) with their mean-age (68.5 ± 3 yrs), mean-disease-duration (104 ± 126.3 months) diagnosed to have Parkinson-and-WC were included in this study. All subjects (right handed) were informed about study and written informed consent was obtained. Five muscles were selected for microelectrode placement, namely ECR, ECU, FCR, FCU were analyzed in all subjects and one more muscle (which showed maximum discordance on mirror-dystonia) of right hand (RH) was included. Mean-amplitudes for right-hand-writing-signal (RHWS) and left-hand-writing-signal (LHWS) for the same muscles though differ significantly in statistical-terms, showed a consistent pattern only in fifth-muscle with larger-mean-amplitudes on left side in all subjects and were not of value in differentiating between concordant (C)/discordant (D) groups-of-subjects. ENMG signals were asynchronously recorded in all 5 muscles while subjects wrote with their RH first (RHWS) and then LH (LHWS). Based on wrist position during writing with RH-and-LH, subjects A1, A7, A11, and A12 fell in the category of 'Discordant' (D) group. The rest 8 were 'Concordant' (C) (for MMs-at-the-wrist).

The principal-component (PC) scores of 12 subject's showed 80% variance in our computation in the scatter plot. The cluster-analysis based on dissimilarity among the subjects' signals show a possibility that, in addition to the grouping of subjects as C or D, some-other-groupings may also be meaningful. ENMG-ENMG coherence was assessed in the Parkinsonism-WC-hand muscles, namely: ECR, ECU, FCR, and FCU, followed by fifth-muscle. The coherence-computed-evaluated and compared between flexor-aspect-of-forearm and extensor-aspect-of-intrinsic hand-muscles was showed significant-coherence in both-groups. These observations-suggest that the nature-of-NNMG-ENMG coherence-in-dystonia WC may be constrained by the descending-motor-systems, both in terms of their anatomical distribution and their frequency-characteristics.

This study showed significant quantifiable EMG differences in the signals seen while writing with the right and left hands between those writer's cramp subjects with concordant mirror movements (C group) versus those with discordant mirror movements (D group). This was mainly seen in the measures of dispersion of the signal i.e., standard dispersion, variances and their ratio (F-ratio). These were statistically significantly different between the two groups, C and D, and the pattern of differences were consistent with the hypothesis that the discordant group had a compensatory force which overcame the dystonic force resulting in the final abnormal posture.

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Hyper-activation of the Rho-GTPase Rac1 via disruption of *ArhGAP15* results in reduced architectural and functional complexity

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The Rho-type small GTPases (Rho, Rac and cdc42) are components of complex signal transduction pathways that link extracellular environmental cues with the control of cytoskeletal dynamic. During brain development, Rac1 plays essential roles ranging from chemotaxis and neuronal migration to neuritogenesis, synapsis formation and plasticity. Rac1 activity is positively and negatively controlled by several molecules, however the role of each specific regulators is poorly known. We have generated mice null for *ArhGAP15*, a Rac1-specific GTPase-activating protein expressed in embryonic migrating interneurons and in a large fraction of both excitatory and inhibitory neurons of the adult cortex and hippocampus. Loss of *ArhGAP15* results in hyper-activation of

Rac1 in the embryonic and adult forebrain, and increased retrograde actin dynamic at the growth cone, associated with defects in neuronal migration, reduced neuritogenesis and reduced spine formation. In spite of a nearly normal cyto-architecture and cortical layering, EEG spectral analysis show reduced high-frequency activity, increased lower frequencies activity, and overall reduced variability. Furthermore, multi-electrode array recordings of spontaneous activity of cultured primary neurons from *ArhGAP15* KO cortex and hippocampus show delayed onset, reduced amplitude, reduced variability and inability to synchronize. Finally we observe motor hyperactivity. Thus a fine modulation of Rac1 activity is required for attaining a proper architecture and function of cortical and hippocampal circuits, and its hyper-activation leads to an Alzheimer spectrum phenotype.

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Brain development behavioural effects after internal ^{137}cesium exposure. GD12 vs postnatal

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Exposure of the brain to ionising radiation at a very young age affects cognitive function, whereas exposure at a later age may adversely affect the cerebrovascular system. *In utero* irradiation in animal models affects brain size and morphology, locomotor and explorative activities, as well as learning and spatial recognition. Evidence that these effects are relevant at low doses comes from pioneering studies that demonstrate that acute prenatal external irradiation in mice changes neurobehavioral performances and brain morphology. Learning disability in children who were exposed in utero in the Chernobyl accident has been reported as well as an increase in Down's syndrome. The aim of this study is to evaluate cognitive ability and neurotoxicological effects that low doses of radiation can cause during in utero and neonatal brain development. C57Bl/6J mice have been exposed to ^{137}Cs, to activities from 0 to 8000 Bq/kg, *in utero* (GD12) or *postnatal* (PND10). Then behavioural tests have been performed at adult age for spontaneous behaviour (including habituation, cognitive functions), Morris water maze and radial arm maze (learning and memory), as well as elevated plus maze (anxiety). The results showed that Caesium low/mid activity exposed animals show an improvement in the working memory, spontaneous behaviour and less anxiety than the other groups of mice irradiated. PND10 irradiated animals show similar behaviour that *in utero* irradiated ones. There appears to be no differences between sexes.

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Neurocognitive effects of exposure to low-dose internal radiation and paraquat in developing offspring mice

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As a result of the nuclear power plants accidents, such as Chernobyl or Fukushima, the population is exposed to external and internal ionising radiation. Human brain is highly sensitive to radiation during foetal and postnatal period when the molecular processes are not completely finished. Previous studies have been shown that exposure to low doses of radiation causes a higher incidence of cognitive impairment. Moreover, exposure to environmental chemicals, such as paraquat (PQ), may potentiate the toxic effects induced by radiation on brain development. The aim of this study was to evaluate the cognitive effects of concomitant exposure to low doses of internal radiation and PQ during neonatal brain development. At the postnatal day 10 (PND10), two groups of mice (C57BL/6J) were exposed subcutaneously to ^{137}Cs at activities of 4000 or 8000 Bq/kg. Two other groups received a subcutaneous injection of PQ (7 mg/200 μL saline) combined with ^{137}Cs at a doses previously described. Finally, control animals received PQ or saline injections during the same period (100 μg/mL). To investigate the spontaneous behaviour, learning, memory capacities and anxiety behavioural tests were conducted in the offspring at 2 months of age. The results showed that cognitive functions were not significantly affected when ^{137}Cs or PQ were administered alone. However, alterations in the working memory and anxiety were detected in mice exposed to ^{137}Cs combined with PQ.

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Age-of-script-acquisition effects in the default-mode network

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According to classic theories of cognition, goal-directed behaviour is organized in the form of scripts that tell us how to attain specific goals, and why they should be attained. The current study is the first to investigate the neural correlates that are associated with processing scripts that were acquired later (vs. earlier) in ontogenetic development. Based on previous evidence that show that the brain's "default-mode network" is characterized by a protracted developmental path, we predicted that activation within this network will be associated with the processing of late-acquired scripts.

In an extensive stimulus-normalization study, participants rated scripts along numerous dimensions (e.g., familiarity, social