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Precongress Course: Neurogenesis and brain repair

24A1
Restorative Neurology. Hopes and perspectives
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Restorative neurology is a new developing branch of Neurology, aiming to the recovery of nervous functions affected by disease or trauma. The concept and accumulated knowledge of neural plasticity have provided a conceptual frame to explain recovery and for the planning of new therapeutic strategies. Developments in basic Neurosciences have lead to new concepts and potential tools intended to improve efficacy of therapy. Neural transplantations have been tested with excellent results in animal models for Parkinson´s Disease. Results in humans have been limited by several factors, particularly the low survival rate of transplanted cells. Trophic factors with actions on nerve cells have been under intensive study during the last decades. Several factors have hindered its clinical application and new strategies are searched to open the ways to clinical practice of this powerful molecules. The most recent development in Neural Sciences have ended with the old dogma of no new neurons in the adult brain. Research on stem cell of neural or non-neural origin represents one of the more promising efforts for the future of Restorative Neurology.

24A2
Stem cells for brain repair
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Brain repair, using restorative approaches such as stem cell neural transplantation holds the greatest promise for the treatment of neurodegenerative disorders and other incurable neurological conditions such as stroke and spinal cord injury. Stem cells are pluripotent and have the capacity to differentiate into neurons and provide us with unlimited neuronal populations of specific phenotypes such as dopaminergic neurons for the treatment of Parkinson's disease. This presentation will explore the concepts of brain repair using stem cell transplantation and intrinsic repair by resident adult stem cells. The potential applications of embryonic, adult and skin-derived stem cells in brain repair strategies for Parkinson's disease, stroke and spinal cord injury will be reviewed. Bioreactor technology for the standardized production of stem cells in large quantities will be discussed. Particular emphasis will be given to neural transplantation techniques and histological analysis of stem cell grafts in the mammalian brain. Behavioral tests used in assessing the ability of stem cells to restore function in animal models of Parkinson's disease, stroke and spinal cord injury will also be reviewed. Finally, the challenges of stem cell research and the potential of translating brain repair strategies using stem cells from the laboratory bench to the clinical setting will be discussed.

24A3
Programmed cell death of adult-generated hippocampal neurons is mediated by the pro-apoptotic gene Bax
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In the dentate gyrus (DG) of the adult mouse hippocampus, several thousand new cells are generated daily, but only a small subset of these survive and differentiate into mature neurons, whereas the majority of the newly generated cells undergo programmed cell death (PCD). However, neither the intracellular machinery required for adult stem cell-derived neuronal death, nor the biological implications of the significant loss of these newly generated cells have been examined. Several markers for apoptosis failed to reveal cell death in Bax-deficient mice, and this together with a progressive increase in neurons number in the DG of the Bax-KO, indicates that Bax is critical for the PCD of adult-generated hippocampal neurons. In Bax-KO mice, doublecortin (DCX)-labeled early migrating neurons were ectopically localized in the hilus, and the majority of the DG neurons failed to express the mature DG neuronal marker, calbindin. Furthermore, in the absence of PCD in the DG, there were age-dependent perturba-

tions of spontaneous locomotor activity in the Bax-KO mice. These results suggest that PCD in the adult brain plays a significant role in the regulation of adult neurogenesis and in its absence some aspects of hippocampal-mediated behavior are affected.

24A4

Neuronal differentiation potential of neural stem cells versus embryonic stem cells

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Recently, enormous interest in neural stem cells (NSCs) has arisen from both basic and medical points of view. Different NSC populations have been identified, which emerge in time and tissue specific manner during development. On the other hand, distinct diseases associated with reduction in specific neuronal populations affecting humans are urgently requiring of therapeutic procedures that use NSCs. The discovery of neurogenesis in the adult brain opens the possibility to induce specific neuronal regeneration from endogenous NSCs. In this regard, characterization of neurogenesis during development will play a fundamental role for the rational design of those therapeutic procedures. In order to study the in vivo differentiation potential of different NSC populations and the influence of the surrounding environment on NSC-specific differentiation, we have designed a system based on the implantation of NSCs in explant cultures of different developing nervous system regions. Our data indicate that NSCs in culture modify its original differentiation potential and that local factors influence their fate. Particularly, we found that neurosphere-derived cells in natural developing environments do not differentiate markedly into neurons, whereas NSCs derived from embryonic stem cells do. Finding the right NSC population and/or the factors guiding its specific differentiation will be the first step for the development of therapeutic procedures based on activation of NSC differentiation. This work is supported by DGAPA and CONACyT.

Precongress course: Assesment and rehabilitation of memory disorders

24B1

Assessment and rehabilitation of memory disorders

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Assessment of memory will be described as a theory-guided process which has to rely on knowledge of brain circuits engaged in time-based (short-term/working memory, long-term memory, anterograde/retrograde amnesia, encoding, storage, retrieval) and contents-based information processing (procedural memory, priming, perceptual, semantic, episodic memory, verbal/non-verbal memory). Furthermore, it will be emphasized that memory should never be assessed in isolation, but has to be embedded in a broad range of additional tests covering personality dimensions, attention and concentration abilities, intelligence, sensory and motor (including language) abilities, etc. The resulting intellectual profile will show preserved abilities and dysfunctions and provides a prerequisite for successful rehabilitation. Concerning rehabilitation, it is again necessary to base this on current theories of memory functioning, for example, on distinctions between implicit and explicit memory training programs (e.g., errorless learning, method of vanishing cues, method of loci, imagery, association learning procedures, internal and external memory strategies in general). Of special importance is that training is generalized to everyday situations and that a proper level of motivation has to accompany the patients' training program.

Precongress course: Speech and reading mechanisms

24B2

Localisation of syntactic and semantic sentence processing using magnetoencephalography (MEG)

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Finnish is a morphologically rich language in which nouns can occur in 15 different cases. Case inflections are used both to signal syntactic (e.g., subject vs. object) relations and semantic (e.g., location in vs. movement from within something) relations. Participants were presented with written sentences that ended in normally inflected nouns, nouns in the wrong case, verbs instead of nouns, or nouns that were correctly inflected but made no sense in the sentence context. The data were analysed in three ways: 1) MEG raw data from nearby channels were averaged to area activations, 2) equivalent current dipoles were modelled, 3) minimum current estimates were modelled. The three methods of analysis supported each other, revealing two major sources of activation correlated with incongruent sentence-ending words. In a time window from 350 to 450 ms, semantically anomalous last words gave rise to the highest activation in the left temporal lobe with clear activation of the same sources also for incorrect word class words and morphological errors. Weaker activation was seen in homologous areas in the right hemisphere. In a later time window, 600–700 ms after word onset, the largest activation was seen to words of incorrect word class and morphological errors at the ends of sentences. Semantically anomalous words did not deviate from correct words in this time window. This activation was localised to more posterior bilateral sources in the temporal lobe.

24B3

Dynamic visual processes in normal reading: implications for developmental dyslexia?

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Data from two studies relating visual task performance to contextual reading are presented. The first study investigated the relationship between contextual reading and, a) relative spatial encoding for symbol arrays, and b) central versus peripheral sensitivity to the frequency doubling illusion. In the first study, thirty school children were measured on their ability to solve a foveally-presented spatial encoding task, as well as their sensitivity to the frequency doubling illusion across the retina. Their performance in the frequency doubling and spatial encoding tasks was uncorrelated, suggesting that these tasks tap independent visual processes. Peripheral (but not central) sensitivity to frequency doubling, and spatial encoding, predicted statistically significant, independent proportions of variance in contextual reading (Neale Analysis of Reading). These effects persisted even when variance due to age, IQ, phonological skill and short-term memory was statistically accounted for. The data suggest that successful reading requires not only information about letter identity, but also at least two additional sources of information, probably related to spatial processing of words. The first is a central mechanism that may define the relative spatial location of letters within words, and the second is a peripheral mechanism that we speculate may be related to the attentional processes involved in coarse-scale localisation within a body of text. Consistent with this speculation, we found in the second study, that reading accuracy for dyslexic readers was most impaired relative to chronological- and age-matched controls when contextual material was presented in whole paragraphs, rather than line-at-a-time or word-at-a-time reading conditions.

24B4

Dissociated semantic access for spoken words and environmental sounds

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Left hemispheric dominance for language processing has long been established. Recently, in an attempt to tease apart the neural substrates involved in manipulating verbal and nonverbal information using Positron Emission Tomography, we have found signs of functional dissociation between the left and the right superior temporal cortices for accessing the meaning of spoken words (Words) and environmental sounds (Sounds), respectively (Thierry, Giraud and Price, 2003, Neuron, 38:499-506). We have then sought converging evidence for the dissociation from Event-Related Potentials (ERPs). In a context of dichotic listening, acoustic signals from the left ear are better received by the right auditory cortex and signals from the right ear are better received by the left auditory cortex. Therefore, when a Word is presented to the right ear while a Sound is presented simultaneously to the left ear (Optimal condition according to the previous PET study), semantic integration should be easier than when the sides of presentation are permuted (Crossed). Fifteen participants were asked to

perform semantic congruency judgement on dichotic pairs of Words and Sounds which had the same meaning or not and which were presented as Optimal or Crossed pairs. We expected to find a classical N400 ERP modulation induced by semantic incongruence and a further N400 modulation for Crossed versus Optimal presentation. We found that N400 peak latencies were delayed by approximately 60 ms for Crossed pairs as compared to Optimal pairs, irrespective of semantic congruency. This is consistent with a functional lateralisation of semantic access depending on stimulus symbolism.

24B5

Lexical stress and sublexical phonology influence spoken word recognition mechanisms: an ERP study

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Theories of spoken word recognition can be divided into two major themes: "sequential" and "goodness of fit." A third class of model proposes that prosodic or stress features of speech are critical for word identification. This study describes research that used ERP to hypothesis test between theories that do or do not account for stress. ERP were recorded to the terminal words of sentences in five conditions: Congruent ("Three people were injured in a highway **ac**cident"); Non-initial stress & prime ("She told the lost tourist to turn right at the traffic po**lite** (light)"; Initial stress & prime ("Eight minus seven equals **won**der (one)"; Non-initial stress/initial prime ("The pirate wore a patch over his **idea** (eye)"; Incongruent ("The spider sat in its web awaiting a **clo**set (fly)." Also, 120 fillers were used ("The girl had long brown **hair**."). Two components, the phonological mismatch negativity (PMN) and the N400, were differentially affected by these manipulations. The PMN to both the Incongruent and Eye/**Idea** conditions differed from each other and were both larger than the PMN seen in the other three conditions. The N400 proved to be sensitive to both stress and sub-lexical phonology with larger amplitudes seen in the Incongruent condition compared to the Eye/**Idea** and One/**Won**der conditions which, in turn, were larger than those seen in the Light/Po**lite** and Congruent conditions. Both the PMN and N400 findings support the importance of word stress in spoken word recognition and its relevance to any theory of spoken word recognition (e.g., the MERGE model).

Precongress course: Face to face with MCI

24B6

Clinical Markers to Predict Progression from Mild Cognitive Impairment to Alzheimer Disease

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Mild Cognitive Impairment (MCI) is an evolving concept in the field of dementia. To date, there is no way to predict which patients with this diagnosis are more likely to progress to Alzheimer disease. The purpose of this retrospective analysis was to examine whether measures of daily function could predict who would progress to Alzheimer disease following a diagnosis of MCI. Methods. Analysis of longitudinal data from patients with the diagnosis of Mild Cognitive Impairment was examined. Variables related to cognitive and functional measures were assessed and, based on conversion status at 2 years, predictor variables were analyzed. Mini-Mental Status Examination total score and Lawton-Brody Instrumental Activities of Daily Living (IADL) and Physical Self-Maintenance Scale (PSMS) subscale and total scores were analyzed.Results. Eight of the patients (40%) progressed to Alzheimer disease over the following 2 years. Subscale analysis revealed that there was a significant difference between groups with respect to their ability to plan and prepare meals ($p<0.05$). This difference was independent of gender. There was no significant difference in age ($p>0.05$), gender ($p>0.05$), or baseline MMSE scores (Conversion = 27.0 vs Non-Conversion = 27.3, $p>0.05$). Total IADL and PSMS scores did not predict conversion. Discussion. Subscale IADL items are more sensitive to change than cognitive screens or total IADL scores. The relative impact of particular IADL's may be lost in Total ADL scores. Outcome scales such as Goal Attainment Scaling of individualized activities may be a more sensitive measurement technique to predict conversion of people with MCI to dementia.

24B7

Mild cognitive impairment – fact or fiction?

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MCI is a clinically significant syndrome, but remains poorly characterised and unlinked to patient perceptions of the impact of the condition. It is generally considered a pre dementia syndrome, but the objective of this paper is to argue that within the current accepted MCI spectrum more than one area of cognition can be demonstrated, functional decline can be measured reliably and patient and carer aspects of life are altered. The methods used are analysis of cognitive testing in controls, MCI patients and AD patients from the memory clinic database, a correlation of the Bayer-ADL scale with a staging instrument and focus groups of patients and informants with both MCI and AD. Results show a spectrum of cognitive impairments, not just memory, increasing in severity even before research criteria standards for dementia are met; significant changes in all items on the Bayer-ADL scale between Global Deterioration Scale 2 and 3 and focus group informants showing under reporting of problems by the patients with MCI – in a manor very similar to that previously described in dementia studies, plus a patient perspective of MCI that mirrors a lot of difficulties faced by those with very mild AD. These results thus suggest that the current definitions of MCI do meet most diagnostic criteria for dementia, and pose the question as to why the "diagnosis" is needed. Several possible explanations will conclude the presentation.

24B8

Self-Administered Mild Cognitive Impairment Touch Screen Tests: The CANS-MCI Study

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This presentation examines the validity of a fully self-administered instrument, the Computer-Administered Neuropsychological Screen for Mild Cognitive Impairment (CANS-MCI), with respect to its ability to provide useful screening information about the need for full diagnostic evaluations of dementia. The CANS-MCI can generate automated graphical reports of longitudinal findings in languages other than those used for test administration and using images that are country-specific. 310 elderly community-dwelling volunteers enrolled in a 3-year longitudinal NIA-funded study in the US. Baseline, and 6-month data are presented. Analyses include confirmatory factor analysis of baseline data on CANS-MCI tests along with concurrent Weschler Memory Scale, WAIS Digit Symbol and Mattis DRS scores. ANCOVAs examined changes at 6-months a, controlling for baseline scores. Results: The validity of the CANS-MCI as a screening instrument for MCI was supported. Confirmatory factor analyses supporting a 3-factor model (Memory, Language/Spatial Fluency and Executive Functioning) provided the basis for testing change scores within cognitive domain factors. Normal and MCI groups for each factor were determined by standardized test scores. Significant group differences over 6 months time were found within each factor for CANS-MCI tests ($p<.05$). Conclusion: The CANS-MCI is an easily administered screening tool measuring all cognitive dimensions that predict the need for treatment. Analyses indicate respectable levels of validity, three primary factors predictive of Alzheimer's, and the ability to distinguish between MCI and normal functioning over time. The CANS-MCI provides change scores that signal the need for full neuropsychological evaluations early enough in the pre-clinical phase of the disease to enhance the timing of treatment decisions.

24B9

Homocysteine: a new risk factor for cognitive decline, vascular and Alzheimer's dementia

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In recent years, the impact of serum tHcy on cognitive function in the older population has started to emerge. Several studies have shown a relationship between tHcy and dementia and between tHcy and cognitive decline associated with aging. Homocysteine is a B-vitamin dependent aminoacid produced during the metabolism of methionine. Elevated tHcy results form low levels or function of folic acid, cobalamin (Clb) or B6, therefore it might be possible to reduce tHcy levels with vitamin therapy, raising the hope for possible preventive treatments. Elevated serum tHcy has been found to be an independent risk factor for the development of Alzheimer's disease. In a recent 8-year follow-up study from the Framingham Study cohort, the authors found that elevated tHcy was an independent risk factor for the development of Alzheimer's disease 8 years after baseline, and that the risk increased with higher levels of tHcy. Similarly, an association between elevated tHcy and dementia has been described in other populations. Results from the UK have shown that serum tHcy levels

are significantly higher among patients with Alzheimer's disease (AD) than in the normal elderly population. In a recent study elevated tHcy was found to be more common among patients with vascular dementia than in patients with AD. Cross-sectional studies in the healthy elderly have yielded conflicting results. Some authors have found significant associations between tHcy levels and cognitive function while others did not. Early studies in a small sample of an Italian healthy elderly population showed no significant correlations between the Mini-Mental State Exam (MMSE) scores and tHcy levels. However, the same authors later found, in a much larger population group, that the risk of lower MMSE scores increased with increasing levels of plasma tHcy, and that tHcy had an independent graded association with cognitive impairment. Cohort studies on the relationship between tHcy levels and scores of cognitive function tests have yielded more consistent results. An early study by McCaddon et al., showed that elevated tHcy at baseline could predict lower verbal and visuospatial deficits at 5-year follow-up. Although initial results from a nested case-control study from the Rotterdam cohort showed no relation between tHcy levels at baseline and decline in scores of the Mini-Mental State Exam (MMSE) (by more than 1 point/year) 2.7 years after baseline, in a population that included younger adults (age >55), follow-up studies from the same Rotterdam cohort showed significant associations between elevated levels of tHcy and scores in a battery of psychometric tests, including the Stroop test, among subjects whose baseline MMSE was lower than 26/30. Recently, in a large cohort study (the Maastricht Aging Study, or MAAS) that included normal subjects 30 to 80 years of age, Teunissen et al found significant correlations between tHcy levels at baseline and scores of tests of cognitive performance, including the Stroop and the Word Learning Test, at baseline and at follow-up. In our cohort study of community living, cognitively normal older adults (with a mean MMSE of 28.4 at baseline and follow-up), we found that tHcy levels at baseline and increases of tHcy levels from baseline to follow-up 2.3 years after, were significantly related to lower scores in the Stroop test at follow-up, independently of other variables, and that the rate of change of tHcy from baseline to follow-up was inversely and negatively correlated with the rate of change in the Stroop scores. Interestingly, declines in the Stroop score were even seen in subjects whose tHcy levels were in the upper range of the normal limit, suggesting that what is considered as "within normal" tHcy levels might already contribute to cognitive deterioration. In conclusion, serum levels of tHcy have been associated with cognitive function in older adults. High levels of tHcy and increases of tHcy over time confer a significant risk of worsening of cognitive function and dementia. There are no published treatment trials aimed at decreasing levels of tHcy, and therefore, it is not known if supplements of B-vitamins can prevent or revert cognitive damage in this population. Given the magnitude of the disease, such studies are warranted.