

<b>Attention and Perception</b>
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**AP1****THE EFFECTS OF V4/TEO LESIONS ON RESPONSES OF MACAQUE AREA TE NEURONS TO TARGETS EMBEDDED IN DISTRACTERS**

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It has been shown that directed attention to a behaviorally relevant visual stimulus can overcome the distracting effects of other nearby stimuli, and physiological studies suggest that the critical attentional mechanisms are located in visual areas of the ventral processing pathway. This idea was tested in a behavioral study of monkeys with "mosaic" visuotopic lesions of extrastriate areas V4 and TEO (De Weerd et al., Soc. Neurosci. Abstr., 1996). In these monkeys, one quadrant of the visual field lacked input from V4, one quadrant lacked input from TEO, one quadrant lacked input from both areas, and one quadrant received normal input. The monkey's ability to discriminate target stimuli presented alone in any of the quadrants was largely unaffected by the lesions. However, if targets were surrounded by distracter stimuli the animal's performance was severely impaired when stimuli were presented in the "lesioned" quadrants, and particularly in the quadrant affected by the combined lesion. These behavioral results lead to the hypothesis that the lesions interfered with mechanisms of selective attention that normally improve the neurons' ability to discriminate between targets by suppressing the influence of the distracters on the responses. As a consequence, the next stage of processing in the ventral pathway, area TE, should receive information about target stimuli in the lesion quadrants that is degraded by the presence of distracters. To test this, we recorded from TE neurons in one of the operated monkeys described above. The monkey fixated a spot at the center of the computer screen and attended to stimuli presented in each of the four visual quadrants, with and without bright white distracters surrounding the targets. Targets were chosen so that they could be either effective ("good") or ineffective ("poor") in driving the neuron when presented alone. The difference in neuronal responses elicited by good and poor target stimuli indicated the amount of useful information available for a behavioral response. Data from 35 neurons suggest that, in parallel with the previously demonstrated behavioral effects of the lesions, the ability of TE neurons to discriminate between targets in the presence of distracters is significantly more impaired when stimuli are presented within the quadrants affected by the lesions than in the normal quadrant. These preliminary results are consistent with the hypothesis that V4 and TEO provide a substrate for integrating visual input with an attentional signal that biases the competition among stimuli in favor of those that are behaviorally relevant.

**AP2****A FUNCTIONAL MRI STUDY OF COVERT AND OVERT ORIENTING OF ATTENTION**

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To identify cortical regions activated during covert and overt shifts of attention, we carried out a functional mapping experiment in which the same subject undergoes tasks of covert and overt visual orienting. Brain activity was measured in 10 right-handed subjects, 5 male and 5 female, using fMRI during the performance of two different types of tasks: 1. Responding to the onset of visual targets (flickering stimuli) presented randomly at unpredictable locations within the visual field while fixating a central square; 2. As in 1., but subjects are free to explore the visual field to detect the targets. Responding to centrally presented stimuli was used as a control task. Irrespective of sex, both tasks of shifting attention evoked largely overlapping patterns of activation. Compared to the central detection task, both the task of covert orienting of attention and the overt orienting task including eye movements significantly increased rCBF ( $p=0.001$ , uncorrected) bilaterally in occipital visual areas (BA 18,19) and in regions of the superior parietal cortex (BA 7). Unexpectedly, subtraction images did hardly indicate significant increases in frontal regions. This may be due to the fact that the control task itself can be interpreted as an alertness task probably also involving primarily right hemispheric structures of a frontoparietal-thalamic network controlling this basic aspect of attention. Thus, contrasting the control task with the two spatial attention tasks may lead to elimination of relevant frontal and parietal activation. In fact, the contrast of the two attention tasks with the OFF-period rest condition (no stimulation) demonstrated more activation clusters in frontal regions (dorsolateral cortical and anterior cingulate) predominantly in the right hemisphere and in parietal cortex. A conjunction analysis across all 10 subjects confirmed the involvement of the areas mentioned in controlling visual orienting in all subjects. The findings are consistent with the frontoparietal network for processes of shifting attention in extrapersonal space reported in former studies. Highly significant increases of activation in occipital regions of visual cortex strongly support the idea of attention-related enhancement of neural activation in cortical areas processing the attended information. The similarity of activation patterns in the two tasks of attention shifting corroborate the results of previous studies that show a considerable degree of anatomical overlap between areas controlling covert shifting of attention and regions active during oculomotor processing. The findings support the existence of a general system for visuospatial attention including both covert and overt orienting.

**AP3****A PET STUDY ON FUNCTIONAL REORGANISATION AFTER TRAINING OF ALERTNESS**

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Recent reports have indicated that there is a specific right hemisphere cortical and subcortical network for intrinsic alertness and sustained attention (1). In a study with patients presenting with right brain vascular damage and deficits of alertness (i.e. percentile rank <25 in the median and/or in the SD of the subtest alertness of the Test Battery for Attention Performance (TAP; 2)), we aimed at assessing changes in the individual functional networks after an intensive specific computerised alertness training. The training, subprogram "Alertness" of the AIXTENT attention training battery (3), was administered for 14 sessions of 45 minutes each. Before and after the training a <sup>15</sup>O-Butanol-PET activation and a comprehensive neuropsychological test battery for attention functions (TAP) and neglect, Behavioral Inattention Test (4), were carried out. In those patients showing behavioral improvement in alertness tasks, the PET activation after the training revealed a partial restitution of the right hemisphere functional network known to subserve intrinsic alertness in normal subjects. Specifically, it seems that a behavioral improvement can be achieved only if the right frontal structures responsible for the control of alertness in normals are reactivated. On the contrary, activation of left brain areas does not lead to a successful recovery of alertness function.

(1) Sturm, W. *et al.* (1999) *Neuropsychologia*, 37, in press; (2) Zimmermann, P. *et al.* (1995) Würselen: Psytest; (3) Sturm, W. *et al.* (1993) Tübingen: G.Narr-Verlag; (4) Wilson, B.A. *et al.* (1987) Bury St. Edmunds: Thames Valley Test Company.

**AP4****HISTOLOGICAL MAPS OF THE HUMAN VISUAL CORTEX IN STANDARD ANATOMICAL SPACE**

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Functional Imaging has indeed yielded a wealth of data regarding the specificity and localisation of brain activation; on the other hand, microstructural characterisation of cortical fields has contributed little to the topography of brain function. Some classical atlases of the cerebral cortex of man remain exquisite models of accurate anatomical observation in the light of clinical and evolutionary issues (1,2). However they cannot efficiently be put to use by the contemporary brain mapping community; this is mainly in view of the limitations intrinsic to two-dimensional charts representing a very limited sample of human brain surface morphological variability. In addition, recent histological studies of the human visual

cortex have not been framed in the same context of data derived from non-invasive brain imaging studies or correlated explicitly with the sulcal geography of individual hemispheres (3,4,5).

We present a parcellation of the human visual cortex in standard anatomical space based on the combined *cyto-* and *myelo-*architectural examination of whole serial sections from occipital and temporal lobes of the human brain. Prior to histological processing an MRI image of the postmortem cerebrum was obtained routinely on a GE Signa LX scanner (at the Dept. of Radiology at the Dartmouth-Hitchcock Medical Center); the sequence was optimised to increase grey-matter / white-matter contrast. The brains were not scanned *in situ* but suspended in a gelatine cast which reproduced the intracranial configuration. Combined histological data that localised architectural fields was coded into voxel values of 3-D MRI representations of the hemispheres (6). The latter were then transformed into standardised stereotaxic space (7) using an automatic registration program which matches the single MRI volumes to the intensity average of 305 MRI brain volumes previously aligned into standardised stereotaxic space (8). Finally, a representation of the cortical surface was extracted to visualise and study the topography of architectural fields relative to the sulcal and gyral surface pattern. We provide standard 3-D co-ordinate ranges for architectonic fields with distinct borders and describe their extent relative to surface cortical landmarks (i.e. the sulcal and gyral pattern). Accordingly, the identity and the localisation of architectural fields in the visual cortex becomes accessible to a comparison with functional imaging data that is defined topographically in the standard co-ordinate system. This cross-analysis is finally indispensable to investigate the relationship between structure and function in the human brain.

(1) Brodmann (1909) Leipzig: Barth (ed); (2) Von Economo, & Koskinas (1925) Vienna: Springer (ed); (3) Clarke & Miklossy (1990) *J Comp Neurol.*, 298:188; (4) Tootell & Taylor (1995) *Cereb. Cortex*, 5:39; (5) DeYoe *et al.* (1990) *Vis Neurosci.*, 5:67; (6) McDonald *et al.* (1994a) in: *Visualization in Biomedical Computing*, 160; (7) Talairach & Tournoux (1988) Thieme (ed); (8) Collins *et al.* (1994) *J. Comput. Assist. Tomogr.*, 18:192.

## AP5

### ATTENTIONAL MODULATION OF COLOR-SENSITIVE CELLS IN MACAQUE VENTROLATERAL PREFRONTAL CORTEX

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Single-unit studies have indicated that many cells in primate prefrontal cortex code the task-dependent meaning of sensory stimuli (e.g., Sakagami and Tsutsui 1999; Kim and Shadlen 1999; Rainer *et al.* 1998; Sakagami and Niki 1994; Watanabe 1992). How do the prefrontal cells convert the sensory information into behavioral commands? To understand the neuronal mechanisms underlying this function, we recorded the activity of cells in the ventrolateral prefrontal cortex. Given that this area receives visual

information directly from the inferotemporal cortex, we expected that it may play a crucial role in converting color information into task-relevant codes. We trained two Japanese monkeys to perform a manual go/no-go task in which they had to use selective attention to one aspect of a compound visual stimulus (a moving random pattern of colored dots) in order to make the correct response. In this task, the monkeys should make a go or no-go response depending on either the color or the motion direction of the compound stimulus. The color of the fixation spot informed the monkeys which visual dimension they should attend to. 10 % of visually responsive cells in the ventrolateral prefrontal cortex (n=14) showed increased activity to a specific stimulus color in both attention conditions (color-intrinsic cells). This activity, however, was modulated to some extent by selective attention, most often enhanced in the color condition. 43 % of the visually responsive cells (n=63) showed differential activity for go and no-go stimuli only when the monkey attended to the color of the compound stimulus, while they responded non-differentially when the monkey attended to the motion direction of the stimulus (color go/no-go cells). The average latency of the visual response was significantly shorter in color-intrinsic cells than in color go/no-go cells. These results suggest that the ventrolateral prefrontal cortex contributes to the behavioral interpretation of color, possibly by means of a sequential process.

## AP6

### VISUAL ATTENTION ENHANCES FUNCTIONAL ACTIVATION IN HUMAN MOTOR AREAS

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Recent results have indicated that attention can modify neural processing (1, 2). Attention heightens awareness to sensory stimuli within a specific modality (3) and it may also generally enhance processing across modalities. Currently, little is known whether generalized or modality specific attention changes mechanisms in the motor system. We investigated if visual attention could enhance hand movement representations in cerebral cortex and cerebellum with functional magnetic resonance imaging (MRI). Nine right-handed healthy young adults performed three button pressing tasks. First, participants pushed a button held in the right hand in response to a visual cue (1 Hz flashing green cross). Second, participants were additionally required to concurrently push a button held in the left hand when a blue cross appeared instead of the green cross (mean frequency = 0.2 Hz, range 2-9 sec). Third, participants pushed a button held in the left hand only when the infrequent visual stimulus occurred. BOLD EPI MR signals were obtained (Siemens Vision 1.5 T) from 20 axially oriented brain slices from the superior convexity to the cerebellum (TE = 64 msec, TR = 3 sec 2 x 2 mm in-plane, 6 mm thick). A block task design was used that alternated button pressing tasks with no-movements; each with equal duration. Correlation methods identified functional MR label. Functional MR labeling occurred mostly in regions commonly activated during repetitive finger movements; these included the primary motor cortex (M1),

supplementary motor area, premotor area, cingulate gyrus, superior parietal lobule, intraparietal sulcus, insula, and the cerebellum. Visual attention increased the extent of movement related MR label in nearly all these motor and premotor regions, especially motor and "non-motor" areas in the cerebellum. However, M1 activation remained unchanged by concurrent visual attention. These results suggest that visual attention modulate movement processing across wide areas of the brain, with the current exception of M1, the cortical area most related to motor performance. The enhancement of activation by visual attention in several non-primary motor cortical areas and the cerebellum provides further evidence that these brain regions contribute to cognitive motor control. The changes in the motor portions of the cerebellum, in contrast to a current lack of effect in M1, may indicate a dissociation between cerebral and cerebellar contributions to motor performance.

(1) Motter (1993) *J. Neurophysiol.*, 70:909; (2) Mc Adams & Maunsell J.H.R. (1999), *J. Neurosci.*, 19:431; (3) Posner *et al.* (1980), *J. Exp. Psychol.*, 109:160.

#### AP7

#### **EVENT RELATED POTENTIAL CORRELATES OF CONSCIOUS AND UNCONSCIOUS VISION IN EXTINCTION**

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Patients with visual extinction lack conscious experience of a contralesional stimulus when it is presented together with an ipsilesional one. It is still unknown at which level of visual processing the contralesional stimulus is lost during extinction. We tried to tackle this problem by recording Event Related Potentials (ERPs) in an extinction patient. A selective alteration of the early visual components of the ERPs would be in favor of an early locus as opposed to a late locus of visual extinction. The patient we studied showed a partial but stable visual extinction as a consequence of a vascular accident in the right hemisphere which involved frontal, parietal, and temporal areas. The partial extinction present in this patient allowed a comparison between different percepts elicited by the same physical stimuli, i.e., between correctly detected bilateral stimuli and bilateral stimuli which were perceived as single ipsilesional stimuli during extinction. We found that the amplitude of the N1 component (one of the early visual components which is modulated by spatial attention) was significantly reduced during extinction and therefore that perception of the contralesional stimulus was lost because of an impairment in the early allocation of spatial attention. As to the mechanisms of this impairment we can consider the possibility of a partial interruption of a prefrontal attentional influence onto extrastriate areas that are important for spatial attention. Such interruption which may be certainly justified by the location of the lesion of our patient would impair perception only during stimulus competition, i.e. during bilateral presentations.

**AP8****EARLY VISUAL VENTRAL STREAM ACTIVITY IN BLINDSIGHT: EVIDENCE FROM ERPS**

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Recent brain imaging studies have reported activations of the ventral visual stream despite V1 denervation of blindsight cases using simple or complex visual stimuli. In this study visually evoked potentials (VEPs) to pictures of human faces were recorded in a blindsight patient (GY). The data suggest that this activity does not originate from visual imagery processes or shape recognition in the dorsal stream, but reflects bottom-up processing of visual stimuli in extrastriate cortex. VEP waveforms, topographical and subtraction analyses support the hypothesis of bottom-up ventral visual stream activity in the V1- deafferented hemisphere. This electrophysiological activity is roughly identical though reduced and delayed as compared to the ERPs recorded when GY is stimulated in the normal visual field. Putative pathways conveying early visual information to extrastriate areas bypassing V1 will be discussed.

**AP9****FAST VISUAL CATEGORISATION OF NATURAL SCENES : ANALOGIES BETWEEN HUMANS AND MONKEYS**

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Neuronal mechanisms underlying cognitive functions are often studied in monkeys with the obvious assumption that the results can be extrapolated to humans, but behavioural strategies in humans and monkeys have rarely been directly compared using the same procedures. In this study, two groups of humans and two macaque monkeys were tested on a visual categorisation task, using the same set-up and stimuli. A succession of natural scenes were briefly presented (30-80ms) on a tactile screen. Subjects started the sequence by pressing a button. They had to release it and touch the screen (“go” response) when the picture belonged to a given target category (either animal or food); otherwise they had to keep pressing (“no go” response). Humans were tested on four blocks of 100 new images. Monkeys were shown daily 10-20 new pictures mixed with familiar ones, and only responses to the first presentation of new images were considered. This study confirmed that humans are slightly more accurate but much slower than monkeys (Thorpe *et al.*, 1996; Fabre-Thorpe *et al.*, 1998), furthermore it suggested that they both categorise natural scenes on the basis of similar cues. Monkeys and humans appeared to have similar difficulties since (i) errors were concentrated on the same images, and (ii) correct go-response reaction times were correlated (both humans and monkeys hesitated for similar stimuli). If they both rely on the same cues, their performance should be similarly affected by the removal of one of them. As

colour may be an important feature for identifying food objects and animals, performance on chromatic and achromatic photographs were compared. The effect of removing colour was only marginal for both species. In humans, the accuracy drop with achromatic photographs was correlated with their reaction time so that colour was a more important feature for humans with long reaction times. Monkeys behaved like the fastest humans showing no impairment with achromatic stimuli. Here again there was a large overlap in errors and reaction times were correlated. Our results show intriguing similarities between monkey and human performance that may have been emphasised by the use of this fast categorisation task. They justify the neurophysiological approach of cognitive functions in monkeys. The mild effect of removing colour could be explained by the fact that, in such a fast categorisation task, decisions could depend on early processing, dominated by the luminance-based (chromatically insensitive) magnocellular stream.

### **AP10**

#### **PERCEPTUAL ASYMMETRIES IN FACIAL AFFECT RECOGNITION FOR HAPPY AND DISGUSTED, CARTOON AND PHOTOGRAPHIC FACES**

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The effects of perceptual asymmetries were examined in a forced choice reaction time (RT) study. University students and residents of the university community (n=51) were exposed to tachistoscopic presentation of cartoon and photographed child faces of happy and disgusted expressions. There was a general RVFA (right visual field advantage) for facial affect recognition. The latency of affect identification was shorter for happy expression than disgusted expression, and photographic stimuli were perceived faster than cartoon stimuli. Performance was generally better for boy's faces than girl's faces. There was a significant interaction effect between modality and gender of stimuli, which indicated that faster perception of photographic stimuli was more prominent with boy's faces than girl's faces. Within 40 female Ss, main effects were also significant for each independent variable, while a significant interaction existed between affect and gender of stimuli. This interaction effect showed that female Ss perceived boy's disgusted expression faster than girl's disgusted expression, whereas girl's happy expression faster than boy's happy expression. Furthermore, 23 right-handed female Ss generally perceived facial affects significantly faster than did 17 left-handed female Ss. When the performance of strongly right-handed Ss (10 males, 11 females, >70 in Edinburgh Handedness Inventory) was analyzed, no main effects were significant, nor were any of the interaction effects. Within-individual analysis revealed that 8 out of 51 Ss showed a RVFA, and that one S showed a LVFA (left visual field advantage). The differences in perceptual dominance had no association with handedness or gender of Ss. Thirty-nine (76%) Ss recognized photographic facial expressions significantly faster than cartoon expressions. Twenty-four (47%) Ss recognized happy expressions significantly faster than disgusted expressions, whereas 5 Ss (10%) demonstrated the opposite tendency significantly. Twelve Ss (4%)

could tell boy's expressions faster than girl's expressions. Previous studies have commonly reported a LVFA for facial affect recognition. In contrast, Stanlans and Wedding (1985) obtained a RVFA, and found that perception of positive affect was faster than that of negative affect. My study also supported a RVFA and a shorter latency for positive over negative expressions. Consistent with the finding of Rhodes and Wooding (1989), photographic faces were perceived faster than cartoon faces. In addition, this current study indicated that gender and handedness factors might intricately underlie affective facial configuration.

Rhodes, G., & Wooding, R. (1989) *Brain & Cognition*, 9 (2), 201; Stanlans, L., & Wedding, D. (1985) *Int. J. Neurosci.*, 25(3-4), 219.

## AP11

### PREFERENTIAL LEFT-EYE USE DURING MIRROR INSPECTION IN FIVE SPECIES OF FISHES

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We recently found that predator inspection is more likely to occur when a companion (i.e, the mirror image of the test animal) is visible on the left rather than on the right side of mosquitofish *Gambusia holbrooki* (Bisazza et al., *Anim. Behav.* in press). This could be consistent with the hypothesis of a preferential use of the right eye during sustained fixation of a predator as well as of a preferential use of the left eye during fixation of conspecifics. Indirect evidence for this has been obtain using detour tests: when faced with a vertical-bar barrier through which a target was visible, female mosquitofish showed a consistent bias to turn left when the target was a predator and to turn right when the target was a conspecific of the same gender. We measured the time spent in monocular viewing during inspection of their own mirror images in females of five species of fish, belonging to different families – *Gambusia holbrooki*, *Xenotoca eiseni*, *Phoxinus phoxinus*, *Pterophyllum scalare*, *Xenopoecilus sarasinorum*. Results revealed a consistent left-eye preference during sustained fixation in all of the five species. These findings add to current evidence in a variety of vertebrate species for preferential involvement of structures located in the right side of the brain in response to the viewing of images of conspecifics.

**AP12****HEMISPHERIC LATERALISATION AND EYE USE DURING SPATIAL TASKS IN THE DOMESTIC CHICK (GALLUS GALLUS)**

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Chicks were trained (with both eyes in use) to find food hidden under a light cap in a square arena, in each corner of which there was a cap. Three conditions were compared: the single baited cap could be identified by position (including cues external to the arena), by colour or by both combined. At test no food was present. Chicks trained with both cues available and tested with one eye in use made more use of colour and less of position when the right eye was used rather than the left. There were no right/left differences in chicks trained with only colour relevant. For chicks trained to use only position, monocular chicks outperformed binocular, perhaps because with both eyes in use, distraction by the sight of a nearby target was more likely. In this condition it was found that the use of an arena with lower walls than normal improved use of positional cues, presumably because extra-arena cues were made more available. One factor, which might produce different performance when using the right or the left eye, in chicks trained binocularly, is preferential use of one or other eye during training. This was studied in chicks which were searching for food in a pot at the end of one of four arms of a cross shaped arena. The pot might be distinguishable from pots at the end of the other arms either by position of the arm or by appearance of the pot. In a series of counterbalanced tests, the chick was placed facing all arms except the baited one. Chicks using positional cues had a bias to turn counterclockwise (ie towards the left visual field), whereas chicks using local cues tended to turn clockwise (to right visual field). Clearly a simple motor bias cannot explain these results. We interpret these findings as showing that reliance on positional cues tends to put the left eye system (LES) in charge, and that this in turn causes the chick to attend to, and turn towards features seen in the left visual field. Reliance on local cues puts the right eye system (RES) in charge and gives the reverse direction of turning. It is likely that such patterns of eye use are one way of sustaining control by one eye system, and one cause of establishment of differing records in RES and LES during binocular learning.

**AP13****PECKING BEHAVIOUR IN PIGEONS WHEN BINOCULARITY IS EARLY KEPT OUT**

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Pigeons possess a panoramic monocular visual field and a binocular frontal overlap varying in size according to the yoked vergence movements, especially effective during pecking. This behaviour is characterised by head fixation stops interspersed with rapid forward head thrusts, during which animals

evaluate extrinsic and intrinsic target's features, since the last pecking phase is ballistic. We are interested in the potential outgrowth of compensating mechanisms used by pigeons on visuomotor control during pecking behaviour when all binocular interactions are kept out *early* and *late* in the life. Pigeons, because of their immature visual system at hatching, represent a useful model for this aim. We analysed the visuo-motor coordination in a Skinner box during pecking at two-dimensional (spot's  $\varnothing = 2; 3.8; 7.6$  mm) and three-dimensional (seed's  $\varnothing = 3.8; 7.5$  mm) targets, in three experimental groups: i) posthatching eye-ball enucleated; ii) adult eye-ball enucleated; iii) control: in binocular and monocular visual condition (adults wearing an eye-patch). The eye-ball was gently drawn away within two days posthatching (or 1 year old) by means of a vacuum pump under deep anaesthesia. All groups were tested one year later. All experimental sessions were videorecorded and the parameters -time of target fixation, distance of target fixation, bill gape and grasp efficiency- were off-line analysed. The main effects were found in the *early* group and the results were the following: i) the visuo-motor coordination to the two-dimensional target showed a remarkable impairment both in the bill gape calibration as well as in peck precision. During the target fixation phase the eye-bill axis was turned contralaterally, and small head movements were frequently present at the small spot. With regard to the visuomotor coordination to the three-dimensional target the grasping efficiency at first hit resulted heavily reduced ( $< 50\%$ ) especially for animals seeing with the left eye. Moreover, the reaching trajectory was always ipsilaterally biased. Finally, the grasping skill remained poor as time went on. ii) As for visuomotor coordination, *late* birds did not differ from the monocular ones. iii) Finally, the control monocular group showed no significant deficit with respect to the binocular vision; moreover, the loss in pecking skill was not so severe. In conclusion, these results show that *early* retinal/extraretinal binocular inputs are essential to build a balanced visuomotor control system, even if in the adult life each eye works correctly by its-self without the help of behavioural compensating mechanisms. On the contrary, the lack of *early* binocular interaction produces some kind of adaptive visuomotor strategies insufficient to a suitable pecking performance.

#### AP14

#### **MULTIPLE IMAGING PROBES REVEAL A SEGMENTAL DEFECT IN THE ANTERIOR FOREBRAIN OF AN ANIMAL MODEL OF HYPERACTIVITY AND ATTENTION DEFICITS.**

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The aim of this project was to investigate putative neural substrates of Attention-Deficit Hyperactivity Disorder (ADHD) in children using the juvenile SHR as animal model. Molecular biological and microscope imaging techniques were used to map the spatial distribution of (i) dopamine (DA) D-1 and D-2 receptor families (by radioligand binding studies), (ii) the  $Ca^{2+}$ /Calmodulin-dependent protein kinase II (CaMKII), and (iii) transcriptional regulators of gene expression such as *c-FOS*, *JUN-B* and *ZIF/268* (by ICC) as markers of neuronal activity in the rostro-caudal plane of the anterior basal forebrain. Computer

assisted high resolution image analysis system revealed in the in the male SHR and Wistar-Kyoto (WKY) rats, an "higher density" of the D-1 and a "lower-density" of the D-3 in a discrete segment of the anterior forebrain only. Moreover, it showed a lower expression of CaMKII in the anterior portion of the n. accumbens pole and shell of the SHR. Transcription factors (TF) revealed a lower constitutive expression in the anterior portion of the shell only, with a differential pattern depending on the specific TF. The data indicate an "*up-regulation*" of D-1 binding sites associated to an "*down-regulation of D-3*" autoreceptors and paralleled by a reduced number of accumbal elements and presumably modules available for limbic-motor integration in a discrete segment. Thus, multiple evidence reveals a defect, that might be due to degeneration of a subset of DA neurons or to a "disintegration" between synaptic inputs and local transcription factors. This in turn, might explain the altered attentional and reinforcement mechanisms demonstrated in the SHR and in ADHD children.

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## **AP15**

### **THE EFFECTS OF NMDA-INDUCED MEDIAL PREFRONTAL CELL LOSS ON THE PARTIAL REINFORCEMENT EXTINCTION EFFECT, SENSORIMOTOR GATING, LOCOMOTOR ACTIVITY AND SPONTANEOUS OBJECT RECOGNITION IN THE RAT**

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The partial reinforcement extinction effect (PREE) refers to the increase in resistance to extinction of an operant response acquired under partial reinforcement relative to that acquired under continuous reinforcement. Prepulse inhibition (PPI) of the acoustic startle response refers to the reduction in startle reactivity towards an intense acoustic pulse stimulus when it is shortly preceded by a weak prepulse stimulus. It has been suggested that these two behavioural paradigms tax two forms of attentional processes, and their dysfunction has independently been linked to the neuropsychopathology of schizophrenia. While PPI reflects an innate early attentional gating mechanism, the PREE is believed to involve the development of acquired inattention towards omission of expected reward. The proposed neural substrates for normal performance in these paradigms appear to overlap considerably, both focus on the importance of the nucleus accumbens and that accumbal function is normally under the modulation of limbic structures, including the medial prefrontal cortex (mPFC). The present study examined the effect of cytotoxic mPFC lesions that typically damaged the prelimbic, infralimbic and the dorsal anterior cingulate areas on the development of the PREE and the expression of PPI in the rat. The lesions led to near complete abolition of the PREE and significant attenuation of PPI. The lesions also increased spontaneous locomotor activity, but this effect appeared to be marginal and transient in nature. On the other hand, these lesioned animals displayed normal preference for a novel object when it was presented jointly with a familiar object which was encountered by the animals ten minutes ago within the

same context. This also served as a test for spontaneous object recognition memory within this delay interval. The present results strengthened the hypothesis that the integrity of the mPFC is critical for the normal development of the PREE and the expression of PPI, possibly via a disruption of ventral striatal function. This suggests that prefrontal dysfunction might be related to the attentional impairment seen in schizophrenia. The sparing of object recognition following mPFC lesions, on the other hand, indicates that mnemonic impairment seen in schizophrenia might be more closely related to temporal lobe neuropathology, rather than prefrontal pathophysiology, associated with the disease.

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#### **AP16**

#### **A DOSE-RESPONSE ANALYSIS OF SYSTEMIC DIZOCILPINE (MK-801) ON PREPULSE FACILITATION, PREPULSE INHIBITION AND SPONTANEOUS LOCOMOTOR ACTIVITY IN THE RAT**

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Prepulse inhibition (PPI) and prepulse facilitation (PPF) are two forms of acoustic startle plasticity in which the reactivity towards a startle-eliciting pulse stimulus is reduced and enhanced by a preceding weak prepulse stimulus, respectively. Disruption of PPI has been associated with the psychopathology of schizophrenia; it has been reported in schizophrenic patients and in rats treated with the noncompetitive NMDA antagonist, dizocilpine (MK-801). The present study was designed to compare the effect of systemic dizocilpine on PPF and PPI at four doses: 0.2, 0.1, 0.05 and 0.025mg/kg. PPI was induced by weak acoustic prepulses of different magnitude (4 ~ 12dB<sub>A</sub> above background) whereas PPF was produced by a visual prepulse in the form of a momentary absence of the test chamber's houselight. In addition, spontaneous locomotion was assessed prior to, and subsequent to, the PPI/PPF test, to evaluate the drug's effect on locomotor activity and stereotypy. The dose-dependent disruptive effect of dizocilpine on PPI was replicated. However, the form of disruption associated with the highest dose was distinct from that of the lower doses. Although clearly attenuated relative to controls, rats treated with 0.1 or 0.05mg/kg of dizocilpine still exhibited significant PPI, and the degree of PPI varied positively with increasing magnitude of the acoustic prepulse. At 0.2mg/kg, dizocilpine completely abolished PPI regardless of the level of prepulse magnitude. At this dose, the animals also displayed characteristic stereotypy during the spontaneous locomotor test. Unlike previous reports, however, dizocilpine appeared to remain effective in attenuating PPI even at the lowest dose (0.025mg/kg). There was little evidence, however, that dizocilpine affected the expression of PPF, except at the highest dose where there was a tendency for diminished PPF. The present study demonstrated that dizocilpine preferentially diminished PPI, and that this attenuation was not accompanied by any systemic effect on PPF. Hence, dizocilpine exerted differential effects on PPI and PPF and this indicated that the drug's action is

unlikely to act at the level of prepulse perception, but subsequent to it. The present data did not support the hypothesis that dizocilpine-induced disruption of PPI might be mediated by a covert enhancement of PPF, and the neuropharmacological profile of PPI and PPF are likely to be distinct.

*Supported by the Conference and Research Grants Council (University of Hong Kong).*

## AP17

### EARLY COMMUNICATION BETWEEN STIMULUS EVALUATION AND RESPONSE SYSTEMS IN A COMPLEX AUDITORY DISCRIMINATION TASK

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In this study we investigate whether the stimulus evaluation system can pass information to the response activation system before completion of the evaluation. Behavioral responses of freely-moving rats were characterized in a decision-making reaction time task. Subjects were first trained in an auditory pitch-discrimination task involving a go/no-go response choice. In a subsequent phase, the two tones used in the previous phase were simultaneously presented in different combinations from two locations. Only the presence of the correct tone from the correct location was predictive of the reward. Another set of rats was trained in a mirror paradigm, in which the subjects were first trained in an auditory localization task involving a go/no-go response choice. In this case the same frequency-modulated sound was presented either from the right or from the left loudspeaker. In a subsequent phase another sound is presented simultaneously, either from the same side or from the opposite side of the apparatus. In this case also the presence of the correct tone from the correct location was predictive of the reward, but the pitch-discrimination followed the place-discrimination task. The observed behavioral strategies suggest a competition between two processes: one involving stimulus evaluation, response preparation and execution, the other involving recognition of the stimulus features associated with inhibition of the go-response. The full time course of the response to conflictual stimuli involving two different tones indicates that the subject has some control over the use of partial information provided by early communication between the stimulus evaluation and the response systems. Furthermore, multiple single units were simultaneously recorded from the temporal cortex of the behaving rats and the search for complex patterns of firing revealed that the onset time of selected patterns was related to the reaction time of the subject. The comparison between the two variants of this paradigm revealed that the succession of the tasks being learned had a deep impact on the performance of the subjects. Our results are compatible with models that postulate continuous flow and asynchronous discrete processing between stimulus evaluation and response activation system. The demonstration of early communication in a complex behavioral task in the rat opens the way to studies of volitional mechanisms in chronic electrophysiological investigation.

**AP18****DISRUPTED AND POTENTIATED LATENT INHIBITION BY SHELL AND CORE LESIONS: THE DUAL ROLE OF THE NUCLEUS ACCUMBENS IN SWITCHING COGNITIVE SETS**

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Latent inhibition (LI) refers to retarded conditioning to a stimulus as a consequence of its prior inconsequential preexposure. LI is disrupted in some subsets of schizophrenic patients and in amphetamine-treated rats, and this disruption has been attributed to enhanced switching to respond according to the stimulus-reinforcement contingency, subserved by the nucleus accumbens (NAC; Weiner, 1990). More recently, we suggested that the switching mechanism resides in the core subterritory and is inhibited by the shell (Weiner et al., 1996). This implies that whereas shell lesion should disrupt LI, core lesion should produce LI which persists under conditions which disrupt the phenomenon in normal rats. Two experiments tested the effects of excitotoxic (NMDA) lesion to the shell or to the core on LI. Both used a two-way active avoidance procedure, but Experiment 2 used either the same or different context in preexposure and conditioning. In Experiment 1, shell-vehicle rats showed LI, i.e., retarded avoidance learning of the preexposed compared to nonpreexposed rats, whereas shell-NMDA rats failed to show LI. In Experiment 2, core-vehicle rats showed LI in the same context conditions, but failed to show LI when the context was changed; in contrast, core-lesioned rats showed LI under both conditions. These results show that LI can exhibit two poles of abnormality, namely, an inability to ignore an irrelevant stimulus (disrupted LI under conditions which lead to LI in normal animals), and an inability to "dis-ignore" an irrelevant stimulus when it becomes relevant (persisting LI under conditions which do not produce LI in normal animals), and that these are subserved by shell and core dysfunction, respectively.

Weiner, I. (1990) *Psychol Bull*, 108, 442; Weiner, I., Gal, G., Rawlins, J.N.P., & Feldon, J. (1996) *Behav Brain Res* 81, 123.

**AP19****TEMPORAL PARAMETRIC DETERMINANTS IN THE PHARMACOLOGICAL DISRUPTION OF PREPULSE INHIBITION OF THE ACOUSTIC STARTLE REFLEX IN RATS**

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Prepulse inhibition (PPI) is the normal reduction in startle reflex that occurs when a startling stimulus (pulse) is preceded by a weak stimulus (prepulse). PPI is reduced in patients with schizophrenia and in

rats after dopaminergic agonist (e.g.: apomorphine) or NMDA antagonist (e.g.: ketamine) injection. However the level of PPI depends on the temporal parameters of the stimuli. In most of the recent pharmacological studies, only a limited number of these temporal parametric conditions have been used to assess PPI and its disruption. There are at least three temporal parameters that can be involved: the prepulse duration (PD), the interval between the end of the prepulse and the beginning of the pulse (PP), and the ratio of these parameters ( $R = PD / PP$ ) with the total interval ( $PD + PP$ ) fixed. In this study, we have used Sprague-Dawley rats to measure PPI under several parametric conditions: for one parameter (PD or PP) the conditions were 5, 20, 80, 160 and 1280 ms, the other parameter (PP or PD) being fixed at 20 ms; for the R parameter the conditions were 2/38, 10/30, 20/20, 30/10 and 38/2 ms (the total interval being fixed at 40 ms). This parametric investigation was conducted for the three parameters under the effect of apomorphine (0.5 mg/kg) and ketamine (6 mg/kg), with control groups injected with saline. In the three saline groups, PPI appeared as non-monotonic functions of each of the parameters. 1/ These functions showed a maximal peak inhibition for the same value of the different parameters, i.e. condition = 20 / 20 ms. 2/ There was no PPI for the condition 1280 ms of the PD and the PP parameters. However the functions of PD and PP looked different. In the six drug groups, apomorphine and ketamine led to an overall reduction of the level of PPI as compared to the saline-treated rats. The PD parameter showed that this reduction was affected differentially by the parameter conditions according to the drug injected. Although apomorphine decreased PPI, the non-monotonic function and the peak inhibition for the 20 ms condition seen in the saline-treated rats were still present. On the opposite, ketamine decreased PPI in a way rather independent of the PD parameter. There was no more peak inhibition at the 20 ms condition and the function was flattened. The results showed that PPI has temporal parametric determinants, especially the prepulse duration, which may have influenced differentially the effect of drugs used to mimic a deficit seen in schizophrenia.

## AP20

### A FUNCTIONAL MRI STUDY OF NEURAL SYSTEMS ENGAGED BY WORKING MEMORY AND SUSTAINED ATTENTION

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The new Tower of London task (TOL) consists in mentally displacing colored balls in order to achieve a goal position. The TOL involves various working memory loads as a function of task difficulty. We compared human cortical activations during the TOL in 3 conditions: "Control" : 0 or 1 move; "Easy": 2 or 3 moves; "Difficult": 4, 5 or 6 moves. Images were acquired using gradient echo conventional sequences in a standard 1.5T Signa (subjects had given their formal written consent). Performance and response time were recorded simultaneously. Our experiments showed that, as compared to the "control"

condition, the "easy" and "difficult" conditions produced significant activations of the prefrontal cortex (superior frontal and precentral sulci), anterior cingulate area and intraparietal sulci. Moreover, when considering individual performances, two groups of subjects emerged : Group 1, with good (> 70%) and stable performance, showed similar activations of the prefrontal cortex during the «easy» and «difficult» conditions. Group 2, with lower (< 70%) and unstable performance, exhibited marked extension in prefrontal activations in both conditions as compared to group 1. In contrast, the two groups did not differ concerning parietal activities. Thus the selective increase in activation of the prefrontal cortex in subjects with lower performance may reflect the cognitive effort required by the task. These results show that the new Tower of London task is suitable for testing prefrontal dysfunction in neuropathologies associated with attentional and working memory deficits.

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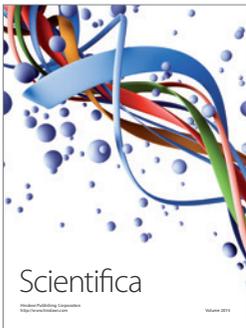
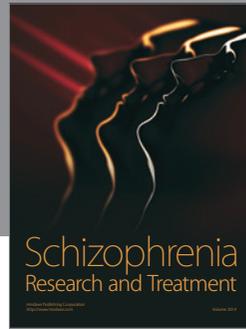
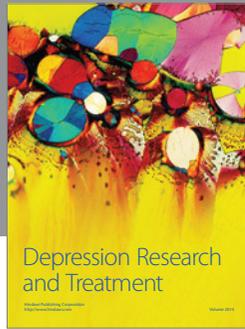
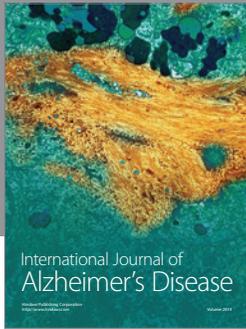
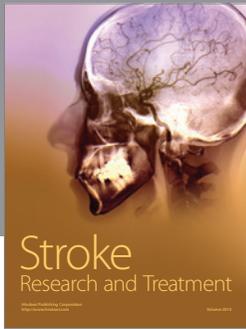
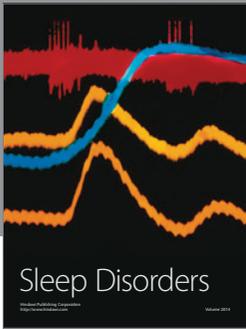
## AP21

### THE HIPPOCAMPUS AND LATENT INHIBITION

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Organisms receiving repeated presentations of a stimulus without consequences subsequently disregard this stimulus when it is followed by significant consequences, e.g., reinforcement. This is manifested in slower conditioning to this stimulus as compared to a novel stimulus and constitutes the phenomenon of latent inhibition (LI). LI is absent in rats and humans receiving the psychotomimetic amphetamine and in acute schizophrenic patients. Neuroleptic treatment restores LI in amphetamine-treated rats and schizophrenics. These results have led to the proposition that LI disruption models a cardinal cognitive deficit in schizophrenia, namely, an inability to ignore irrelevant stimuli. Consistent with the temporal lobe pathology implicated in schizophrenia, it has been shown that conventional hippocampal lesions disrupt LI. However, we recently found that total transection of the fornix fimbria left LI intact.<sup>1</sup> The present experiments investigated further the involvement of the hippocampus in LI using excitotoxic lesions and stimulation with NMDA. Lesioning the dorsal, ventral or the entire hippocampal formation with NMDA was without an effect on LI as assessed in two procedures, conditioned emotional response (CER) in rats licking for water and two way active avoidance (2WAA). In the 2WAA procedure there was a trend towards enhanced LI following the complete hippocampal lesion. However, using stimulation of the ventral hippocampus with a low dose of NMDA (0.7µg/0.5µl, bilaterally) we found attenuated LI in the CER procedure. These results indicate that increased hippocampal activity plays a role in LI disruption, but the hippocampus is not necessary for LI expression. We obtained a similar differentiation between hippocampal lesions<sup>2</sup> and stimulation<sup>3</sup> in another model of attentional deficits associated with



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