ARTICLES

BAZIN N, BRUNET-GOUET E, BOURDET C, KAYSER N, FALISSARD B, HARDY-BAYLE MC, PASSERIEUX C.
Quantitative assessment of attribution of intentions to others in schizophrenia using an ecological video-based task: a comparison with manic and depressed patients.

Schizophrenia is characterized by the impairment of several facets of social cognition. This has been demonstrated in numerous studies that focused on specific aspects of social cognition such as the attribution of intentions, emotions, or false beliefs to others. However, most of these studies relied on complex verbal descriptions or impoverished social stimuli. In the present study, we evaluated a new task (Versailles-Situational Intention Reading, V-SIR) that is based on video excerpts depicting complex real-life scenes of social interactions. Subjects were required to rate the probabilities of several affirmations of the intentions of one of the characters. The V-SIR task was administered to schizophrenic patients (N=15), depressed patients (N=12), manic patients (N=15), and healthy controls (N=15). The performance of schizophrenic patients was significantly impaired in comparison to healthy and depressed subjects. There was a trend toward a significant difference between schizophrenic and manic patients. Manic patients also demonstrated impaired performance relative to healthy subjects. Schizophrenic patients' V-SIR scores were significantly correlated with their scores on another attribution of intentions task that used comic strips. These results show that tasks based on more ecological stimuli are powerful enough to detect theory-of-mind abnormalities in pathological populations such as schizophrenic patients

Chronic high dose transdermal nicotine in Parkinson's disease: an open trial.

Whether nicotine has therapeutic effects on Parkinson's disease (PD) symptoms is controversial, but high doses and chronic treatment have never been tested. We report the results of a pilot, open-label trial to assess the safety and possible efficacy of chronic high doses of nicotine. Six patients with advanced idiopathic PD received increasing daily doses of transdermal nicotine up to 105 mg/day over 17 weeks. All patients but one accepted the target dose. Nausea and vomiting were frequent but moderate, and occurred in most of the patients (four of six) who received over 90 mg/day and 14 weeks of nicotine treatment. During the plateau phase, patients improved their motor scores and dopaminergic treatment was reduced. These results confirm the feasibility of chronic high dose nicotinic treatment in PD but warrant validation of the beneficial effects by a randomized controlled trial.

Although we have shown in three out of five patients with Huntington's disease that motor and cognitive improvements 2 years after intracerebral fetal neural grafts are correlated with recovery of brain metabolic activity in grafted striatal areas and connected regions of the cerebral cortex, neural grafts are not known to have protective effects on the host brain per se. We undertook long-term follow-up of previously reported patients with the disease to ascertain the nature and extent of any secondary decline after grafting.

METHODS: Five patients with Huntington's disease from our pilot study were assessed annually with the unified Huntington's disease rating scale, neuropsychological tests, and MRI, for up to 6 years after neural grafting. Resting cerebral activity was recorded at 2 and 6 years.

FINDINGS: Clinical improvement plateaued after 2 years and then faded off variably 4-6 years after surgery. Dystonia deteriorated consistently, whereas chorea did not. Cognitive performance remained stable on non-timed tests, whereas progression of motor disability was shown by deterioration on timed tests. Hypometabolism also affected the brain heterogeneously, sparing the benefits in the frontal cortex and at the precise location of the grafts, but showing a progressive deterioration in other areas. Two patients who had no benefit from grafting at 2 years continued to decline in the same way as non-grafted patients.

INTERPRETATION: Neuronal transplantation in Huntington's disease provides a period of several years of improvement and stability, but not a permanent cure for the disease. Improvement of the surgical procedure and in patient selection could improve the therapeutic value, but neuroprotective treatment seems to be unavoidable in the disease.

Neuroprotective gene therapy for Huntington's disease, using polymer-encapsulated cells engineered to secrete human ciliary neurotrophic factor: results of a phase I study.

Huntington's disease (HD) is a monogenic neurodegenerative disease that affects the efferent neurons of the striatum. The protracted evolution of the pathology over 15 to 20 years, after clinical onset in adulthood, underscores the potential of therapeutic tools that would aim at protecting striatal neurons. Proteins with neuroprotective effects in the adult brain have been identified, among them ciliary neurotrophic factor (CNTF), which protected striatal neurons in animal models of HD. Accordingly, we have carried out a phase I study evaluating the safety of intracerebral administration of this protein in subjects with HD, using a device formed by a semipermeable membrane encapsulating a BHK cell line engineered to synthesize CNTF. Six subjects with stage 1 or 2 HD had one capsule implanted into the right lateral ventricle; the capsule was retrieved and exchanged for a new one every 6 months, over a total period of 2 years. No sign of CNTF-induced toxicity was observed; however, depression occurred in three subjects after removal of the last capsule, which may have correlated with the lack of any future therapeutic option. All retrieved capsules were intact but contained variable numbers of surviving cells, and CNTF release was low in 13 of 24 cases. Improvements in electrophysiological results were observed, and were correlated with capsules releasing the largest amount of CNTF. This phase I study shows the safety, feasibility, and tolerability of this gene therapy procedure. Heterogeneous cell survival, however, stresses the need for improving the technique.

BOURDET C, BROCHARD R, ROUILLON F, DRAKE C.
Auditory temporal processing in schizophrenia: high level rather than low level deficits?
COGNITIVE NEUROPSYCHIATRY,. 2003 May;8(2):89-106.

INTRODUCTION: Patients with schizophrenia demonstrate a wide range of information processing deficits. Most recent studies argue in favour of high level deficits, including attention and context
processing, whereas fewer studies have demonstrated deficits at earlier stages of processing, such as perceptual discrimination and organisation. This is the first study to investigate both high and low level processing, within a single paradigm, in the case of auditory temporal processing in schizophrenia.

METHODS: Patients with schizophrenia were compared to controls on a series of tasks involving three auditory temporal processes varying from low to higher level: (1) segregation of a complex sequence into component auditory streams; (2) detection of local temporal irregularities within a stream; (3) attentional focusing on one stream by the use of a cue preceding the complex sequence.

RESULTS: The lowest level of processing examined here--stream segregation--appeared to function equally well in patients as in controls. However, the higher level processes--irregularity detection and attentional focus--functioned in both groups, but less efficiently in patients with schizophrenia.

CONCLUSIONS: Results demonstrate abnormal auditory temporal processing in schizophrenia. Abnormal performances only in Processes 2 and 3 support and hypothesis of higher level rather than lower level processing deficits in schizophrenia.

LEFAUCHEUR JP, BACHOUD-LEVI AC, BOURDET C, GRANDMOUGIN T, HANTRAYE P, CESARO P, DEGOS JD, PESCHANSKI M, LISOVOSKI F.

Clinical relevance of electrophysiological tests in the assessment of patients with Huntington's disease.

Assessment programs recently designed to follow-up patients with Huntington's disease (HD) in therapeutic trials have not included electrophysiological testing in the list of mandatory examinations. This omission is likely due to the current lack of data establishing a clear correlation between the electrophysiological results and those of clinical assessment. We address this issue in a cohort of 36 patients at relatively early stages of the disease (I and II). Electrophysiological studies comprised the recording of palmar sympathetic skin responses (SSRs), blink reflexes (BRs), thenar long latency reflexes (LLRs), cortical somatosensory evoked potentials (SEPs), and electromyographic silent periods evoked by transcranial magnetic stimulation (SPs). Results were analyzed with reference to disease duration and staging and to specific cognitive, psychiatric, and motor alteration. SEPs were the most and very sensitive markers, because they were abnormal in 94% of patients. Except for LLRs, alteration of electrophysiological results increased in parallel to the evolution of the disease. Except for LLRs and SSR latency, electrophysiological results correlated with those of specific clinical examinations. In particular, an increased BR latency or a reduced amplitude of the N20 component of SEPs correlated with the extent of bradykinesia, whereas a reduced amplitude of SSRs or of the N30 component of SEPs correlated with hyperkinesia. Overall, electrophysiological tests, in particular SEPs and BRs, appeared sensitive and interesting in the follow-up of HD patients and correlated with various clinical parameters, suggesting that these easy to perform and noninvasive repeatable examinations could be added fruitfully to the assessment programs for HD.


Motor and cognitive improvements in patients with Huntington's disease after neural transplantation.
BACKGROUND: Huntington's disease is a neurodegenerative disease of genetic origin that mainly affects the striatum. It has severe motor and cognitive consequences and, up to now, no treatment. Motor and cognitive functions can be restored in experimental animal models by means of intrastriatal transplantation of fetal striatal neuroblasts. We explored whether grafts of human fetal striatal tissue could survive and have detectable effects in five patients with mild to moderate Huntington's disease.

METHODS: After 2 years of preoperative assessment, patients were grafted with human fetal neuroblasts into the right striatum then, after a year, the left striatum. Final results were assessed 1 year later on the basis of neurological, neuropsychological, neurophysiological, and psychiatric tests. The results obtained were compared with those of a cohort of 22 untreated patients at similar stages of the disease who were followed up in parallel. Repeated magnetic resonance imaging (MRI) and positron emission tomography (PET) scanning with fluorine-18-labelled fluorodeoxyglucose was also done to assess metabolic activity.

FINDINGS: The final PET-scan assessment showed increased metabolic activity in various subnuclei of the striatum in three of five patients, contrasting with the progressive decline recorded in the two other patients in the series, as seen in patients with untreated Huntington's disease. Small areas of even higher metabolic activity, coregistering with spherical hyposignals on MRI were also present in the same three patients, suggesting that grafts were functional. Accordingly, motor and cognitive functions were improved or maintained within the normal range, and functional benefits were seen in daily-life activities in these three patients, but not in the other two.

INTERPRETATION: Fetal neural allografts could be associated with functional, motor, and cognitive improvements in patients with Huntington's disease.


Safety and tolerability assessment of intrastriatal neural allografts in five patients with Huntington's disease

This study describes issues related to the safety and tolerability of fetal striatal neural allografts as assessed in five patients with Huntington's disease. Huntington's disease (HD) is characterized by motor, cognitive, and behavioral disturbances. The latter include psychological disturbances and, as a consequence, we took particular care to analyze behavioral changes, in addition to the usual “safety” follow-up. We conducted multidisciplinary follow-up at least 2 years before and 1 year after grafting. Psychological care extended to close relatives. The grafting procedure itself was altogether safe and uneventful, and there were no apparent clinical deleterious effects for 1 year. The immunosuppressive treatment, however, was complicated by various problems (irregular compliance, errors of handling, side effects). Direct psychological consequences of the transplantation procedure were rare and not worrisome, although mood alteration requiring treatment was observed in one patient. Indirectly, however, the procedure required patients and relatives to accept constraints that tended to complicate familial situations already marred by aggressivity and depression. All patients and close relatives expressed major expectations, in spite of our strong and repeated cautioning. It is clearly important to be aware of these particular conditions since they may eventually translate into psychological difficulties in coping with the long-term clinical outcome of the procedure, if not beneficial. Despite an overall good tolerance, therefore, this follow-up calls for caution regarding the involvement of HD patients in experimental surgical protocols.


Neuroprotective gene therapy for Huntington's disease using a polymer
encapsulated BHK cell line engineered to secrete human CNTF

Huntington's disease (HD) is an autosomal dominant genetic disease with devastating clinical effects on cognitive, psychological, and motor functions. These clinical symptoms primarily relate to the progressive loss of medium-spiny GABA-ergic neurons of the striatum. There is no known treatment to date. Several neurotrophic factors have, however, demonstrated the capacity to protect striatal neurons in various experimental models of HD. This includes the ciliary neurotrophic factor (CNTF), the substance examined in this protocol. An ex vivo gene therapy approach based on encapsulated genetically modified BHK cells will be used for the continuous and long-term intracerebral delivery of CNTF. A device, containing up to 10^6 human CNTF-producing BHK cells surrounded by a semipermeable membrane, will be implanted into the right lateral ventricle of 6 patients. Capsules releasing 0.15-0.5 microg CNTF/day will be used. In this phase I study, the principal goal will be the evaluation of the safety and tolerability of the procedure. As a secondary goal, HD symptoms will be analyzed using a large battery of neuropsychological, motor, neurological, and neurophysiological tests and the striatal pathology monitored using MRI and PET-scan imaging. It is expected that the gene therapy approach described in this protocol will mitigate the side effects associated with the peripheral administration of recombinant hCNTF and allow a well-tolerated, continuous intracerebroventricular delivery of the neuroprotective factor.

GRANDMOUGIN T., BOURDET C., GURRUCHAGA JM
De la danse de Saint-Guy à la chorée de Huntington : rappels sur l’émergence d’un concept médical.
MÉDECINE & SCIENCES, 13, 1997, 850-4

BOURDET C., OLAVARRIA J., VAN SLUYTERS R.C.
The distribution of visual callosal neurons in normal and strabismic cats.

It has been suggested that synchronous activation of cortical loci in the two cerebral hemispheres during development leads to the stabilization of juvenile callosal connections in some areas of the visual cortex. One way in which loci in opposite hemispheres can be synchronously activated is if they receive signals generated by the same stimulus viewed through different eyes. These ideas lead to the prediction that shifts in the cortical representation of the visual field caused by misalignment of the visual axes (strabismus) should change the width of the callosal zone in the striate cortex. We tested this prediction by using quantitative techniques to compare the tangential distribution of callosal neurons in the striate cortex of strabismic cats to that in normally reared cats. Animals were rendered strabismic surgically at 8-10 days of age and were allowed to survive a minimum of 18 weeks, at which time multiple intracortical injections of the tracer horseradish peroxidase (HRP) were used to reveal the distribution of callosally projecting cells in the contralateral striate cortex. HRP-labeled cells were counted in coronal sections, and data from four animals with divergent strabismus (exotropia) and four with convergent strabismus (esotropia) were compared to those from four normally reared animals. Although our data from strabismic cats do not differ markedly from those reported previously, we find that the distribution of callosal cells in
the striate cortex of these cats does not differ significantly from that in our normally reared control cats. These results do not bear out the prediction that surgically shifting the visual axes leads to stabilization of juvenile callosal axons in anomalous places within the striate cortex.

BOURDET C, CESARO P
Bases neuroanatomiques et fonctionnelles de la psychiatrie : cortex préfrontal, schizophrénie.

L'importance prise par le lobe frontal chez l'homme et les primates incite à étudier ses dysfonctionnements, et ce d'autant plus que sa partie antérieure, ou préfrontale, n'est directement connectée à aucun système moteur ou sensoriel. Connecté à des structures sous-corticales et à d'autres aires corticales non " primaires " le cortex préfrontal participe à des fonctions élaborées d'organisation et de contrôle des comportements. Sa pathologie neurologique induit différentes perturbations cognitives et cette symptomatologie est variable en fonction du degré de maturation cérébrale au moment de la lésion. Les données de l'expérimentation animale (morphologique, physiologique et comportementale) et celles de la clinique neurologique assorties à une meilleure connaissance de l'ontogénie et de la plasticité cérébrales ouvrent à un abord sémiologique et conceptuel nouveau de la pathologie psychiatrique. L'hypothèse développementale de la schizophrénie en est un exemple illustrateur. L'application en psychiatrie de techniques de la psychologie cognitive d'une part, et le développement de techniques d'explorations anatomofonctionnelles utilisables in vivo d'autre part, permettent d'explorer ces voies dans le champ de la psychiatrie.

DESCE J.M., BOURDET C,
Dossier : Du nouveau du côté de la recherche en Psychiatrie ?
LA LETTRE DES NEUROSCIENCES, 1994, n°7

BOURDET C., GOLDENBERG. F.
Insomnia in anxiety : sleep EEG changes.
JOURNAL OF PSYCHOSOMATIC RESEARCH, Vol. 38, Suppl. 1, 1994, pp. 93-104

Anxiety is often paired with sleep disturbances and both interact in a quite complex manner. Sleep (and vigilance) problems are often included in the descriptive definition or in the diagnostic criteria for anxiety disorders. Nevertheless, if anxiety may cause sleep disturbances, it is also known that sleep deprivation may produce symptoms which fall within the symptom complex of anxiety. In this paper, some of the methodological issues encountered when studying sleep and anxiety are discussed. Polygraphic recordings of sleep in anxious patients have consistently shown an increased sleep latency and, quite often, also exhibited a reduced sleep time, a reduced total sleep time, less slow-wave sleep, a greater arousal index and an increased duration of wakefulness during sleep. From our own study, we also report anomalies of the first night cycle in anxious poor sleepers who are otherwise indistinguishable from normal controls (with regard to the 'classical' sleep parameters). We have also observed the large interindividual variability
of numbers of sleep parameters in anxious people. The question of a potential heterogeneity of the studied groups with regard to their clinical presentation as well as their sleep profile has been raised through our research as well. It is apparent that strategies for exploring the source of the potential heterogeneity of anxiety disorders are still needed.

ONTENIENTE B., MORELLOU P., NEVEU I., MAKEH I., SUZUKI F., BOURDET C., GRIMBERG G., COLIN P., BRACHET P., MALLETT J., BRIAND P., PESCHANSKI M

Cell-type-specific expression and regulation of a c-fos-NGF fusion gene in neurons and astrocytes of transgenic mice.

MOLECULAR BRAIN RESEARCH, 21, 1994, 225-234

A mouse line transgenic for nerve growth factor (NGF) was developed using the mouse prepro-NGF cDNA inserted within a plasmid containing the proximal region (-10 to -550 bp) of the c-fos promoter and the transcription termination and polyadenylation signals of the rabbit beta-globin gene. No significant modification of gross behavior or central nervous system anatomy was detected in adult animals as assessed by immunohistochemistry and in situ hybridization for NGF and choline acetyltransferase. The expression of the transgene and the possible regulation of its expression by agents acting on the promoter were investigated in vitro. Despite the presence of an additional pool of NGF mRNA specific to the transgene, basal levels of NGF in the supernatant of transgenic astrocytes were similar to normal ones. On the other hand, transgenic neurons spontaneously synthesized and released levels of NGF two to three times higher than normal neurons, while mRNA levels were barely detectable by conventional Northern blotting. The tissue-specificity of NGF expression was respected, with higher levels in hippocampal than neocortical neurons. Increases of NGF mRNA by agents acting on the promoter could be observed in normal and transgenic astrocytes only after inhibition of the protein synthesis by cycloheximide, suggesting a similar rapid turnover of normal and transgenic transcripts. Cyclic AMP agonists specifically increased the secretion of NGF protein by transgenic astrocytes and neurons, while activators of the protein kinase C had a similar effect on transgenic and normal cells. Differences between amounts of NGF secreted by neurons and astrocytes with regards to their respective content in mRNA suggest that transgenic transcripts are subject to normal cell- and tissue-specific post-transcriptional regulations. Agents acting on the c-fos promoter through the protein kinase C or cyclic AMP routes differentially increased the secretion of NGF by transgenic astrocytes or neurons, supporting this hypothesis.

DERLON J.M., BOURDET C., BUSTANY M, CHATEL P., THÉRON J., DARCEL F., SYROTA A.

11C-L-Méthionine uptake in gliomas. [PET-Scan study]

NEUROSURGERY, vol.25 n°5, 1989, 720-728

Treatment of gliomas remains disappointing in spite of a great number of experimental biological data and of randomized therapeutic studies. This could be partly explained by the inefficiency of our conventional methods to assess the regional metabolism of these tumors. The use of positron emission tomography (PET) brings encouraging possibilities in this field. We report our preliminary experience of measuring regional cerebral methionine uptake with PET after intravenous injection of [11C]L-methionine. Twenty-two patients with histologically confirmed gliomas were studied. An ECAT II positron emission tomograph was used for scanning. The position of the plane was chosen to
include a major section of the tumor in the reconstructed brain slice. The protocol required a two-step examination: 1) after injection of 15 to 25 mCi of [11C]L-methionine, 12 scans were performed over a period of 46 minutes; and 2) 18 hours later, regional cerebral blood volume was measured in the same slice after intravenous injection of 2 to 4 mCi of 68GaCl3. The tumoral region of interest was determined as being the area of maximum activity. For each patient we calculated the ratio, R, between the activity in this tumor region of interest and the activity in the contralateral healthy symmetric region of interest which was used as an "internal standard" for the same patient. We correlated the ratio R with the histological grading. In 22 patients, mean values of R were calculated for each tumor: Grade II (n = 5): R = 1.04 +/- 0.27; Grade III (n = 5): R = 1.68 +/- 0.22; and Grade IV (n = 12): R = 2.33 +/- 0.86.

BOURDET C., DEHAY C., KENNEDY H
Characteristics of inter- and intrahemispheric transient pathways in the young kitten.

CHAPITRE D’OUVRAGES


In CHATEL M, DARCEL F, AND PECKER J Brain Oncology biology, diagnosis, and therapy / an International Meeting on Brain Oncology, Rennes, France, September 4-5, 1986 ; held under the auspices of the Ministry of National Education, the University of Rennes, and the Regional Hospital Rennes, 1987, Pays Bas: Edition Martinus Nijhoff Publishers, pp 179-183