# Report on the ECNP Meeting "Neuropsychopharmacology across Brain Diseases", held in Nice, France from 9 to 10 March 2010.

Authors: David Nutt[1], Sven Ove Ögren[2], Jan M. van Ree[3]
[1]Imperial College London, United Kingdom; [2]Karolinska Institute, Stockholm, Sweden; [3]Rudolf Magnus Institute of Neuroscience, Utrecht, The Netherlands

[Programme of the meeting can be found at the ECNP website: http://www.ecnp.eu/about-ecnp/history/past-ecnp-meetings/past-stand-alone-meetings/~/media/Files/ecnp/history/stand%20alone%20meetings/ECNP_Meeting_programme.ashx]

This meeting brought together a selected group of psychiatrists, neurologists, and basic scientists to present the latest important developments in drug discovery and therapeutics for brain disease and to stimulate expert discussion on major problems in modern neuropsychopharmacology under different angles. In eight sections, composed of a lecture by each of the three professional disciplines and a discussion session, themes of common interest were covered like the use of anticonvulsants, dopamine (DA) enhancing drugs, deep brain stimulation and gene therapy. This summary of the meeting aims to be relevant for all participating disciplines.

## 1. Anticonvulsants/mood stabilisers

Eduard Vieta (Spain) discussed the use of anticonvulsants in bipolar disorder (BPD). BPD is a recurrent condition that has similarities with epilepsy (cycling nature, unpredictability of crisis, and some shared treatments), but different physiopathology and epidemiology. Mood stabilisers are drugs which treat mania or depression or both and/or are active in prevention of their recurrence. The antiepileptic drugs carbamazepine and valproate do have mood-stabilizing properties particularly in the control of mania, and lamotrigine is active in relapse prevention of depressive episodes, but others, like gabapentin and topiramate, are not effective in BPD. The mechanism of action behind those different potencies in BPD is not well understood; anticonvulsant drugs with related biochemical properties may or may not be effective mood-stabilisers. The development of anticonvulsants has been guided by rather predictive animal models for epilepsy, but animal models for BPD are very poor, and drug development in this area has been mainly based on serendipity. However both epilepsy and BPD are recurrent conditions that come in episodes, and show increased frequency and severity with recurrence (increased allostatic load). This pattern fits with the kindling model that has been used to explain common pathways in the mechanism of action of anticonvulsant drugs. Recently, an FDA meta-analysis of clinical trials pointed out that there could be a signal of increased suicidality with some anticonvulsant drugs when compared to placebo, while drugs like lithium may have anti-suicidal effects. In the FDA report, this risk was larger in epilepsy than in BPD, perhaps because suicidality was less effectively excluded from clinical trials in epilepsy. In fact, naturalistic data suggest that bipolar patients *responding* to anticonvulsants may actually have decreased suicide risk when compared to untreated patients, so any signal related to suicidality may have to do with non-responders and with the underlying condition.

Matthias Koepp (UK) reviewed new anticonvulsants and concluded that despite the significant number of new antiepileptic drugs (AEDs), there is little difference between new and conventional AEDs in their outcome. In chronic epilepsy, the impact of new AEDs is slight at best with about 10% achieving seizure-freedom with levetiracetam, topiramate or lamotrigine. The development of AEDs has either been through serendipity (sodium valproate, levetiracetam, and topiramate), secondary use of psychiatric medications (phenobarbitone, carbamazepine) or modification of existing medication (oxcarbazapine, eslicarbazepine). The few AEDs that have been "rationally" designed have either been withdrawn because of intolerable risks and side-effects (vigabatrin) or are largely ineffective in epilepsy (gabapentin, tiagabine). New AEDs are tested in the same animal models, which have been developed to treat seizures, but not the underlying condition or type of epilepsies, resulting in "me-too" drugs. The pathophysiology and molecular basis underlying epileptogenesis, i.e. the development of an epilepsy condition and progression thereafter, are complex and still largely unknown. New or truly antiepileptogenic drugs are still needed and new paradigms for the assessment of potential novel therapies need to be developed. Currently old targets are revisited including the GABA-ergic system, NMDA receptors modulation, and novel approaches such as local drug delivery are being explored. Also in-vivo assessments of mechanisms of drug resistance with imaging of p-glycoprotein (P-gp)

function is now possible, which will allow better characterisation of patients and prediction of treatment response.
Some patients who develop drug resistance appear to have increased P-gp pump activity so extrude the AED from the brain. Koepp noted that siblings of epileptic patients may be a good endophenotype for epilepsy, as they do share genetic factors, but are asymptomatic. The same type of studies are being performed in other indications, like schizophrenia and Alzheimer's disease.

Guy Goodwin (UK) argued that in the search for novel, improved therapeutics for mood disorders, the study of genetic risk factors and moderating/acquired factors might overcome the shortcomings of current mainly phenomenological thinking, which focus on symptoms and lacks underlying neurobiological models and endophenotypes of mood disorders. Risk factors in mood disorders are family history, temperament, early abuse and neglect. Moderating factors are life events, physical illness and alcohol and drugs use. As Kendler et al (2004) detected neuroticism as risk factor in depression. Goodwin studied the possible endophenotypical correlates (neuropsychological and functional brain imaging) of high versus low neuroticism in healthy volunteers, and demonstrated a negative appraisal bias in those with high neurotic scores, which is accompanied with changes in relevant neuronal networks. Current antidepressants seem to affect those neuropsychological processes. On the other hand in this type of experiments in students with BPD there were a different and a positive response bias from higher risk taking behaviour in a gambling task leading to more negative experiences. He suggests that at present research on cognitive processes probably gives best access to specific functional systems to study relevant mechanisms in psychiatric illness, which may help and speed up discovery of new treatments.

## 2. Dopamine function enhancing drugs.

David Heal (UK) presented a scientific rationale for efficacy and safety in the pharmacotherapy of attention deficit hyperactivity disorder (ADHD). Intracerebral microdialysis experiments in rodents have revealed that the most effective drugs *d*-amphetamine and methylphenidate increase the synaptic concentrations of noradrenaline (NA) and dopamine (DA), not only in the prefrontal cortex , but also in important subcortical brain regions like the striatum. Their action to increase the extracellular concentration of catecholamines is rapid, substantial and without dose effect ceiling. It is therefore very probable that the combined enhancement of dopaminergic and noradrenergic function in the brain plays a critical role in the mechanism of action of the most effective ADHD drugs. On the other hand, the powerful pharmacodynamics of the stimulants that delivers efficacy in ADHD by potentiating central dopaminergic function is also responsible for their liability for abuse.
In microdialysis experiments comparably high levels of extracellular dopamine (DA) can be produced by administration of methylphenidate or d-amphetamine, but not by conventional DA reuptake inhibitors like GBR 12909, suggesting that the action of methylphenidate cannot be explained by reuptake inhibition and it probably also has a rapid releasing effect on DA and NA.
These findings are of potential interest to neurologists because dopamine reuptake transporter (DAT) imaging is now a widely used clinical and research tool. DAT imaging is usually performed with radioactively labelled cocaine derivatives or methylphenidate. At present it is unclear whether chronic dopamine treatment in Parkinson's disease (PD) induces regulatory changes in DAT and thus affects imaging results in longitudinal studies (esp. neuroprotection trials).

Walter Pirker (Austria) discussed the role of DA agonists (DAag) as replacement therapy in PD. In contrast to the DA precursor levodopa, which provides most effective control of motor symptoms, but often results in the development of motor complications (motor fluctuations and dyskinesias), DAag do not require enzymatic conversion in degenerating DA neurons and directly stimulate postsynaptic DA receptors. DAag improve motor function and reduce motor fluctuations in advanced PD. DAag also became the first-choice treatment of early PD after randomized controlled trials with a duration of up to 5 years show that early monotherapy of PD with DAag delays the onset of motor complications, but these benefits may be lost over time. Also, despite some preclinical evidence for neuroprotective properties, clinical studies failed to demonstrate that DAag treatment delays the progression of disability in PD. Recent studies do suggest that DAag (for example pramipexole) are mildly effective in the treatment of the very common PD depression. Compared to levodopa, DAag are characterized by less improvement in motor function and higher rates of side effects including daytime sleepiness, hallucinations and rather frequently impulse control disorders (e.g. gambling, excessive shopping and hyper-sexuality seen in about 10% of patients).

It was commented that these impulse control disorders are worth exploring as they give a new insight into addiction uncomplicated by prior illicit drug use and could help expose vulnerability factors – specifically the role of pre- versus postsynaptic DA function predicting addictive behaviours. It seems that younger patients with a trait for sensational seeking behaviour are particularly vulnerable and clinicians should be cautious when prescribing DAag to PD patients with this personality trait. It seems rational that psychiatrists and neurologists meet regularly to evaluate symptomatologies in patients with ADHD or PD.

Per Svenningsson (Sweden) further explained the receptor characteristics and potentials of DAag. While levodopa acts both on D1 and D2 receptors (D1R, D2R), DAag more specifically target the D2R-like class (D2R, D3R, D4R), and thus D1R probably is related to the disturbing motor fluctuations. D2-like receptors do have additional qualities which could offer opportunities for further improvement in therapy, in particular D2R form heterodimers with several other receptor type (D3R, A2A, CB1, Glu, ionchannel blockers, etc.); thus drugs with combined activity may offer new therapeutic opportunities, like D2R agonist plus adenosine 2A antagonists. Also it is now clear that D2R signal via both G-protein-dependent and –independent signalling pathways. The G-protein-independent pathway involves a complex formed by beta-arrestin/AKT and regulates GSK-3 signalling. At the moment the relative contribution of these signalling pathways in mediating anti-Parkinsonian actions are unclear and it is envisioned that biased agonists at either one or the other pathways may have improved efficacy.

David Nutt (UK) mentioned, that the role of DA in reward is probably limited to stimulant-type drugs presumably because the DA reuptake site is their immediate pharmacological target; while studies from his group with heroin and nicotine and others with fentanyl and cannabis revealed no DA release (Daglish et al 2008). But if DA is not central to reward then what does it do in addiction? Preclinical studies indicate that it may relate to the desire for or expectation of drug effects and there is some limited data that support this in relation to food desire. And if DA is not central to reward then what neural systems subserve this? The most likely candidate seems to be the endogenous opioid system which is clearly the target for heroin and which seems to be stimulated “downstream” by stimulants and alcohol.

## 3. Cognition Enhancers

Thomas Bayer (Germany) discussed translational aspects in Alzheimer’s disease (AD). Besides tangles, *extra*cellular amyloid plaques are the postmortem landmark of AD. However, results from longitudinal studies like the Nun-study, showing cases with an abundance of such brain pathology without dementia, question the toxicity of these extracellular plaques and their relatedness to the striking region specific neuron loss, like pyramidal neurons in the entorhinal cortex and CA1 neurons in the hippocampus. There is accumulating evidence demonstrating that *intra*neuronal amyloid beta 42 (Aβ42) triggers early synaptic deficits and neuron loss. Among other interesting mouse models for AD, APP/PS1KI mice show early intraneuronal aggregation of full-length and N-terminal modified Aβ42 peptides. In this model the time point of loss of long-term potentiation, disrupted paired pulse facilitation and hippocampus-dependent deficits in learning and memory behaviour correlates with CA1 neuron loss and hippocampus atrophy. The APP/PS1KI model is so far the model with the most aggressive pathology. Also data obtained on transgenic mice that overexpressed pyroglutamate Aβ peptide, shows localized cerebellar neuronal loss and atrophy without plaque formation. These data demonstrate that both synaptic deficits and neuron loss are a consequence of intraneuronal accumulation of Aβ peptides. Inhibition of intracellular APP maturation and stabilization may offer new opportunities for therapeutic intervention in Alzheimer’s disease.

In the discussion topics were identified for which our current knowledge is severely lacking:
1. Synaptic plasticity; What role does synaptic plasticity play in maintaining normal cognitive function in the face of the challenges of the ageing process? Is age-related dementia simply a reflection of impaired synaptic plasticity which can be mediated by a number of the common pathological causes (i.e. AD, dementia with Lewy bodies and vascular pathology) and many rarer forms of pathology?
2. Function of apolipoprotein E (APOE): it is more than 15 years since the discovery was made that APOE genotype is the major risk factor for sporadic AD, accounting for at least half of the genetic risk. This indicates that APOE has crucial functions in the brain in preventing and/or causing the disease. Although there is evidence implicating APOE in deposition and removal of Aβ aggregates and also in

mediating lipid transport in the brain, essential for maintenance and repair of neuronal cell membranes and synapses, we still don't fully understand how APOE is relevant.
3. The normal function in the brain of Aβ is still unknown. It is crucial to know this as many current therapeutic strategies are aimed at reducing production of Aβ or enhancing elimination of Aβ. Is it safe to do this or will there be unacceptable side effects?

## 4. Opioids

Mu opioid receptors, which are distributed throughout the nervous system, mediate the potent analgesic and addictive properties of the opioids morphine and heroin.

Wim van den Brink (The Netherlands) showed that opioid addiction is a chronic relapsing disorder and that different treatment strategies are available, including strategies directed at stable abstinence from all opioids using opioid antagonists and strategies directed at abstinence of illicit opioids using opioid substitution. Strategies directed a stable abstinence include the following steps: motivation, detoxification and, most important and most difficult, relapse prevention. The opioid antagonist has been used for relapse prevention but long term effects have been disappointing due to low retention rates and low compliance. However, new naltrexone formulations are now available with sustained periods of action: naltrexone intramuscular injections (1-2 months) and naltrexone implants (3-6 months). Naltrexone has also shown to be effective in the treatment of alcohol and amphetamine dependence and in the treatment of pathological gambling, but not in nicotine dependence. In alcohol dependence, the response to naltrexone seems enhanced in subjects with favourable variations in mu-opioid receptors (OPRM1). In cases where stable abstinence is not attainable, successful pharmacological tools are available to reduce or stop the use of illicit opioids and restrict the long term consequences of opioid addiction using agonist replacement (methadone or buprenorphine) or therapy with controlled use of the drug itself (heroin assisted treatment).

Michael Ossipov (USA) summarized the major role of the opioid system in pain processing, where morphine still remains the most effective compound to treat pain, in spite of numerous attempts to develop more efficacious drugs. However it has been commonly held that opioids are not effective against neuropathic pain, but this is not an accurate assessment, as numerous studies, both with i.v. and oral administration, demonstrated reasonable efficacy of morphine, fentanyl or oxycodone in several neuropathic pain states. The critical factor is that the doses required to achieve adequate pain relief will produce high incidences of adverse effects, like constipation, nausea and somnolence, along with “cloudy thinking”. These adverse effects are tolerable with effective treatment of acute pain, but become intolerable with chronic use (50% premature stopping). Also there is a need for increasing doses of opioids to maintain pain relief, i.e. there is antinociceptive tolerance. This tolerance is related to the paradoxical enhancement of pain sensitivity, which has been demonstrated in healthy volunteers after a few days of dosing with morphine and occurs in patients as well. Unfortunately, this tolerance phenomenon is sometimes erroneously interpreted as a sign of drug misuse.

Katia Befort (France) studies the genetic adaptations to chronic drug use. Earlier experiments with various drugs in knockout mice for mu-opioid receptors demonstrated the role of these receptors in drug reward and dependence. The central extended amygdala (EA), a network formed by the central nucleus of the amygdala and the bed nucleus of the stria terminalis, is found to be a key site for the control of craving and drug seeking behaviours. Following 6 days of morphine administration in mice, and using Affymetrix microarrays to analyze transcriptional activity in this specific brain structure, i.e. EA, they identified about one hundred genes for which expression was specifically modulated by activation of the mu-opioid receptor from wild-type but not mu-in-opioid receptor knockout mice (Befort et al 2008). It was further tested whether regulation of these genes occur in response to chronic treatments with prototypical non-opioid drugs of abuse, including nicotine, THC or ethanol, whose rewarding properties are strongly dependent on the mu-opioid receptor. Clustering analysis highlighted groups of genes displaying profiles of up- and down-regulation uniquely regulated by one drug or commonly regulated by two or three out of the four drugs. In the same paradigm after 4 weeks of abstinence from morphine groups of genes with various expression patterns across dependent and abstinent groups were demonstrated (Le Merrer et al 2011).

Although opioids are recognised as unsurpassed analgesics for moderate to severe pain, Guy Simonnet (France) indicates that for more than a century clinical studies have reported that hyper-

responsiveness to noxious stimuli is the most common symptom of withdrawal after prolonged opioid administration. More recently, this paradoxical phenomenon, named opioid-induced hyperalgesia (OIH), has been reported to develop rapidly in animals, human volunteers and surgical patients following initial opioid exposure (Angst and Clark 2006). It is now recognised that OIH reflects a sustained sensitisation of the nervous system, in which excitatory amino acid neurotransmitter systems play a critical role, especially via NMDA receptors (Célèrier et al 2001). These observations suggest that tolerance observed after an acute or repeated opioid administration is partly the by-product of a pain sensitization process induced by opioids and that it is the enhancement of pain sensitivity that creates the need for a higher dose to maintain the therapeutic effect. New therapeutic strategies capable of preventing the development of pain sensitization would then be effective in preventing the development of tolerance to analgesic effects of opioids.

## 5. Neurostimulation techniques

Deep brain stimulation (DBS) for movement disorders has been widely applied since 1987. The most frequent indications are Parkinson disease, tremor, and dystonia respectively, and until now about 40.000 patients have been treated with DBS. The risk of the implantation has become as low as less than 2%, thanks to the improvement of imaging and planning techniques. Because of this large experience the indications have been expanded to psychiatric disorders. These include obsessive-compulsive disorder (OCD), major depression (MDD), Gilles de la Tourette's syndrome, and most recently addiction. Preclinical research plays an important role in defining the most optimal target for each specific indication.

As explained by Damiaan Denys (The Netherlands), the use of DBS in psychiatric disorders has received great interest owing to the small risk of the operation, the reversible nature of the technique, and the possibility of optimizing treatment postoperatively. However a reliable judgement on its therapeutic value in disorders like OCD is hampered by the lack of well-controlled clinical trials. Preliminary results (obtained in about 75 patients) suggest that DBS in OCD can effectuate a decrease of 40–60% in severity of symptoms in half of the patients, with best results obtained from stimulation in nucleus accumbens, ventral striatum and subthalamic nucleus (STN). Although various adverse effects occur, most of these are transitory. Possible disadvantages of DBS are the relatively high costs, risk of brain surgery (bleeding), need for replacement of battery in chest, limited clinical evidence and the lack of long term data. The mechanism of action of DBS in OCD is unknown. The speed of the effect of DBS causes fundamental questions on the pathophysiology of psychiatric disorders, i.e. where serotonergic drugs needs weeks to get effective in OCD, DBS (with proper settings) may improve symptoms within minutes though this is not always the case.

Trevor Sharp (UK) explained how animal research contributes to our understanding of the neurobiological mechanism of action of DBS regarding beneficial as well as adverse effects. Originally, the beneficial effects of DBS on the motor symptoms of PD patients have been related to the inhibition of neurons in the STN, because in animal models of PD, DBS had the same effect as STN lesions or chemical inhibition of the STN. Current data suggest that the source of the anti-PD effects of STN-DBS is antidromically activated afferent axons from the cortex resulting in modulation of basal ganglia neural networks and the jamming of pathological oscillations therein.
In about one third of the operated patients STN-DBS leads to problematic behavioural changes, mainly impulsivity and depression. In animal studies STN-DBS inhibited the firing of neurons in the midbrain raphe nuclei (Temel et al 2007) and also significantly decreased extracellular serotonin (5-HT) levels in both striatum and medial prefrontal cortex. In further experiments they found that STN-DBS elicited a 5-HT-dependent, mood-related behavioural change (increased helplessness) that was prevented by SSRI administration. So STN-DBS had a direct influence on the dorsal raphe and its serotoninergic output, which are probably relevant for its adverse behavioural effects. It is unknown whether similar mechanisms explain the effects of DBS when applied in other regions, but the knowledge gained from the application of DBS in PD is clearly laying the foundation for its use in other therapeutic areas. Present attempts to introduce closed-loop stimulation in PD, in which pathological neural activity is sensed by external devices and triggers stimulus onset (brain-machine interfaces), as well as improved DBS hardware (e.g. longer battery life) are examples of technological developments that are relevant to DBS use in other disorders.

Andrea Malizia (UK) noted that unlike movement disorders, psychiatric disorders are more difficult to model adequately preclinically, thus we are more reliant upon human observations for progress. Therefore all patients undergoing DBS should also take part in detailed mechanistic studies, which should include systematic reporting on electrode location, stimulus characteristics and also of adverse effects and concurrent treatments. In addition MRI tractography with description of the relationship between specific contacts and white matter connectivity, neuropsychology  especially if combined with brain imaging  and pharmacological testing perhaps combined with receptor imaging are thought to be useful tools.

## 6. Genetics and connectivity.

Anthony Baily (UK) presented relevant data on autism, that is one of a large diagnostic cluster of Autism Spectrum Disorders (ASD), characterized by impaired social interaction and communication problems, which also include Asperger's and Rett syndrome, and have a prevalence of about 1%. Important associated features are mental retardation (75%) and epilepsy (25%), anxiety, depression and anorexia, and a higher presence in males. ASD is a complex disease with great variance in behavioural manifestation (=phenotype), with multiple genetic risk factors. There are no effective drug treatments for the core symptoms of the disease. Although in relatives there is a higher incidence of social dysfunction, the search for candidate genes has not been very successful. There are chromosomal abnormalities found, particularly at 15q11-13, related to GABRB3 and UBE3A. Although there is a hypothesis of synaptic dysfunction in autism, genetic evidence of relevant abnormal gene expression is sparse. Genetic parametric linkage studies, as well as association studies found indications for abnormalities in genes related to cortical development. Neuro-pathological findings in ASD reflect substantial (10%) enlarged brain size, evidence for abnormal neuronal migration (inferior olive nuclei), cortical abnormalities in glia/neuron ratio and laminar profiles. Imaging studies using MRI indicate changes in the localization and differentiation of stimulus-related activation (faces versus other objects) and changes in white matter integrity. But as a whole it is unclear to what extent ASD is characterized by increased or decreased neural connectivity or both in different areas.

Mart Saarma (Finland) presented on neurotrophic factors and connectivity problems in neuro-degenerative diseases. In Parkinson's disease DA neurons located in the substantia nigra and making synapses to the striatum progressively degenerate and die. Growing evidence suggests that DA neurons first lose synapses, followed by axonal degeneration and cell death. Currently all available PD treatments are symptomatic and unable to slow down or stop neurodegeneration. Genes mutated in PD families are rarely linked to cell survival, but more to basic biochemical processes of protein folding and transport thus leading to problems with axonal functioning and maintenance. Neurotrophic factors are important for the maintenance of neurons and during trauma they protect and repair neurons. Regenerative properties of neurotrophic factors are based on their ability to stimulate neurite outgrowth and synaptogenesis. Glial cell line-derived neurotrophic factor (GDNF) and its homologous protein neurturin are able to protect and repair of DA neurons in animal models of PD. However, GDNF and neuturin diffuse very poorly into brain tissue and GDNF did not prevent the alpha-synuclein-induced DA neurodegeneration in the genetic rat model of PD. Part of these limitations may be overcome by using the recently discovered neurotrophic factor (see Lindholm et al 2007). Cerebral dopamine neurotrophic factor (CDNF) and its homologous protein mesencephalic astrocyte-derived neurotrophic factor (MANF), together with the invertebrate homologous protein, form a novel family of evolutionarily conserved neurotrophic factors. CDNF and MANF can protect and repair midbrain DA neurons in rodent models of PD more efficiently than any other known neurotrophic factor. CDNF and MANF diffuse much better in the rodent brain tissue than GDNF and in addition have a unique property to bind oxidized phospholipids and may also enhance protein folding. Both characteristics may counteract neurodegeneration also in PD.

Raul Gainetdinov (Italy) discussed the aberrant functional connectivity in genetic animal models of hyperdopaminergia and NMDA receptor hypofunction, which are both seen as potential underlying pathological mechanism of schizophrenia. The potential contribution of various neurotransmitter systems to particular endophenotypes of schizophrenia has been investigated in genetically modified animal models. The DAT gene knockout mice (DAT-KO) provide a model of hyperdopaminergia, as there is excessive extracellular DA (and almost no storage). The DAT-KO-mice display hyperactivity, perseverations in cognitive tasks and deficient sensorimotor gating. These behavioural deficits can be corrected by antipsychotic drugs and as such recapitulate particular endophenotypes of schizophrenia related to positive symptoms. The deficits are also affected by moodstabilizing compounds, which may

be related to the DA/Akt/GSK3 pathway. NR1 mutant mice, which carry a hypomorphic allele of the NR1 subunit of the NMDA receptor, provide a model for a hypoactivity of the glutamate system and display a more complex set of behavioural abnormalities that include mild hyperactivity, social dysfunctions, deficient sensorimotor gating and cognitive impairment. These aberrant behaviours can be ameliorated more effectively by atypical rather than typical antipsychotics and thus NR1 deficient mice may have translational value to understand endophenotypes of schizophrenia related to negative symptomatology. These genetic animal models of aberrant connectivity may be instrumental to decipher the contribution of specific neurochemical abnormalities to certain endophenotypes of schizophrenia and other psychiatric disorders.

## 7. Antidepressants

Erkki Isometsä (Finland) explained that after the first antidepressants were discovered by serendipity in the 1950s, the number of antidepressants has expanded, but while side effects diminished, almost all have broadly similar monoaminergic mechanisms and equal efficacy. Efficacy of many antidepressants has been demonstrated in both depression and anxiety disorders, and several related conditions. There is also a high genetic linkage between as well as substantial (57%) comorbidity of those conditions, suggesting some shared neurobiological basis. Limited efficacy and slow onset of action are key problems in antidepressant treatment. The STAR*D study, initiated by NIMH, which subsequently tested four different phases of treatment extension, demonstrated a cumulative remission rate of 67% (Rush et al 2006). Strategies commonly used in clinical practice to increase effects include sequential trials with different antidepressants, drugs with multiple mechanisms of action; combining potentially synergistic antidepressants, or augmenting antidepressants with lithium, atypical antipsychotics, or thyroid hormone. Agomelatine is a new antidepressant with novel mechanisms of action involving agonism of melatonin receptors plus antagonism of $5HT_{2C}$ receptors. I.v. ketamine and i.v. scopolamine have been found in small randomized controlled trials to have robust and rapid antidepressant action, raising hopes of finding glutamatergic or perhaps anticholinergic drugs with rapid onset of action. The hypothalamus-pituitary-adrenal (HPA) axis, particularly glucocorticoid receptors or CRH-1 are other promising targets. Other areas investigated include neurotrophic or anti-inflammatory mechanisms.

Jill Rasmussen (UK) reviewed the use of antidepressants in post-stroke depression, which is a significant problem occurring in about 40% or people who have had a stroke. It has important implications for cognitive and functional outcomes, with patients in whom depression is treated showing greater motivation and compliance with their rehabilitation programmes and greater improvement in activities of daily living. Known risk factors are: neuroticism, psychiatric disorder in family and negative life events in last six months, and their impact is cumulative. In post-stroke depression benefit from treatment has been seen with different classes of antidepressants – SSRIs, TCAs, mirtazapine –, and the risk / benefit profile seems to be similar to that in MDD, although numbers studied are relatively small. Antidepressants are effective in both preventing post-stroke depression and treating emergent depressive symptoms. Treatment should be continued for at least 2 years if optimal prevention of depression is to be achieved.

In addition to stroke there are a range of other neurological disorders where depression is very significant e.g. early Alzheimer's disease, Parkinson's disease, multiple sclerosis where depression is often precipitated by one of the key treatments interferon, and in epilepsy. In general there is a need to further investigate the similarities and differences between depression in psychiatric patients and depression associated with these neurological disorders, whether the mechanisms of depression are similar, whether traditional antidepressants work in each condition as well, etc.

Eero Castrén (Finland) explained the relationship between antidepressants and neural plasticity. The brain stores and processes cognitive and emotional information in neuronal networks, which are formed during early postnatal critical periods, in a process where genetic and environmental information interacts. Nerve growth factors (NT-3, NT-4, BDNF) play an essential role in the formation of informative contacts and thus to establish neural networks. Abnormal early environment may produce lasting effects on the structure and function of networks and the limited plasticity of adult networks impedes efforts to rewire the abnormal networks later in life. Antidepressants do affect BDNF in hippocampus; in BDNF-knock out mice the effect of ADs in the forced swim test is reduced, while transgenic mice over-expressing BDNF have a stronger antidepressant effect in the model, so in

a sense antidepressants are “neurotrophic drugs”. In an elegant series of experiments (see Maya Velencourt et al 2008), using mammalian visual cortex as a model of formation and plasticity of well characterized networks, it was demonstrated that chronic antidepressant treatment reopens critical period plasticity and leads to adaptive reorganization of a network miswired by abnormal early environment (deprivation of vision in one eye). Thus when antidepressant drug treatment is combined with environmental rehabilitation it could help open up maladapted neural circuits usually not accessible for reorganization (see Castrén and Rantamäki 2010).
This is generally recognized to be an exciting approach, where known antidepressants have a measurable impact on neurotrophic signalling pathways, even though it is still controversial whether antidepressant efficacy is achieved through a modulation of cellular plasticity and if cellular plasticity or neurotrophic stimulation per se could produce antidepressant effects.

Enrico Domenici (Italy) summarized that the development of innovative therapies for depression poses a number of significant challenges at the different steps of the drug discovery process. Depressive disorders are rather complex diseases both from a genetic and a neurobiological standpoint, which, combined with their high level of heterogeneity, makes the identification of molecular targets a difficult task. In addition, the paucity of animal models that are able to inform on the neural circuitry of depression is a significant obstacle to the validation and progression of novel therapeutic approaches (see Krishnan and Nestler 2008). In the clinics, the lack of objective tools to diagnose and monitor the progression of the disease usually results in a need of large and complex trials in order to detect antidepressant efficacy. A potential improvement may arise from the enrichment of phenotypic characterization of the patients by complementing the diagnostic assessment with biological and instrumental markers (see CW Turck (ed.) 2008).

## 8. Gene Therapy

Frank Kooy (Belgium) discussed the fragile X syndrome, which is the most common form of inherited mental retardation. It is the consequence of absence of the FMR1 gene, which binds and regulates many other genes in the cell. The function of this gene has been intensively studied in mouse and fruit fly models of the disorder. The group discovered that GABA-ergic signalling is disturbed in the brain of fragile X animal models. This finding is of a special interest, as GABA(A) receptors are the main inhibitory receptors in the brain and play a role in anxiety, depression, epilepsy, insomnia and learning and memory. As these processes are disturbed in the fragile X syndrome as well, they hypothesized that an altered composition of the GABA(A) receptor may play a role in the behavioural aspects of the fragile X syndrome (Heulens et al 2010). It was shown that FMRP, the protein product of the FMR1 gene, binds various subunits of the GABA(A) receptor, in line with a disturbed transportation or regulation of GABA-ergic mRNA in the absence of FMRP. PET scans using labelled flumazenil, an antagonist of the GABA(A) receptor, indicated that the GABAergic system is downregulated in fragile X syndrome patients just like in animal models. Preliminary experiments indicate that neurosteroids, a specific class of drugs that bind to the GABA(A) receptor, prevent the occurrence of seizures in fragile X syndrome mice, which may have therapeutic promises for this disease.

Anders Björklund (Sweden) reviewed the use of recombinant lentivirus and adeno-associated virus (AAV) vectors for gene delivery to the brain, and as a tool for gene therapy in Parkinson´s disease. The recombinant AAV (rAVV) vectors are particularly promising for this purpose since they transduce very efficiently neurons into the adult brain; they are essentially free of viral genes and not known to be associated with any human disease; also they cause no inflammatory/immune reactions in the brain. In PD the aim is to deliver genes for one or more of the essential enzymes for producing L-DOPA from tyrosine – tyrosine hydroxylase and GTP cyclohydrolase – and/or DA from L-DOPA (DOPA decarboxylase). Optimal expression of genes may enhance and stabilize availability of DA in the striatum, which is thought to be important for the protection against L-DOPA-induced motor disturbances. Single, dual and even triple gene approaches are under investigation and impressive results have been obtained in MTPT-lesioned monkeys (see Jarraya et al 2009); but for some of the vectors optimal titers may be difficult to realize in man. The Lund group studies the use of rAAV for delivery of the enzymes involved in the production of L-DOPA in animal models of PD, and they produced a targeted, continuous delivery of L-DOPA in the striatum, which can completely restore motor function, and prevent the development of L-DOPA-induced dyskinesias in rodent models of PD.

William Wisden (UK) presented the biology of AVVs and how recombinant versions (rAAV) are a leading tool for gene delivery in basic research and gene therapy (see Burger et al 2005). The

advantages of rAAVs include: long term transgene expression; no destructive T cell responses; safe to use in the lab. The native AAV genome contains two gene sets: Rep and Cap. In rAAV, these genes are removed, and replaced with a transgene, so that the genome is: ITR-transgene-ITR. The rAAV coat proteins (which confer the serotype) can be changed to promote transduction of different cell types. For adult neurons, a serotype of AAV1/AAV2 works best. To get the transgene expressed in specific neuronal types researchers use rAAV transgenes that contain flex switches (Atasoy et al 2008). The transgene is in reverse orientation and cannot be expressed. However, if the rAAV is injected into Cre driver mouse lines, in which Cre is expressed in particular subsets of neurons, although the rAAV will infect all cell types, it can only express its transgene in cells which express Cre. This elegant method ensures cell-type selective gene expression of rAAV in mice (Murray et al 2011).

Several of the speakers mentioned the possibility of making neurons light-sensitive using "optogenetics" (Fiala et al 2010), which would enable specific subtypes of neurons to have their activity controlled in a very precise manner. To make such human neurons light-sensitive, they would need to express a light-sensitive ion channel or pump gene. The rAAV vectors would be a very promising way of delivering this gene.

## Concluding remarks

The theme of the meeting on Neuropsychopharmacology across Brain Diseases was rather broad, and many different viewpoints were expressed, but further cross-talk among disciplines can only help expand the ways of formulating ideas and open discussions across fields. We should encourage this type of meeting in neuroscience as it brings about every contributor to view his/her own work differently and it enables in-depth assessment of the challenges involved in the dynamic and fast moving fields of drug discovery and therapy. It is vital to link basic research within the context of clinical applications and not to lose sight of therapeutic application, as well as to bring feedback from clinical neurology and psychiatry into the development of the theories on brain disorders and their treatment.

## Acknowledgements:

The input by Cor Sennef, PhD, Consultant Clinical Neuroscience, in the preparation of this document is highly appreciated.

The following persons were present at the meeting **and** contributed to this report:
Thomas Bayer, Germany; Katia Befort, France; Anders Björklund, Sweden; Eero Castrén, Finland; Damiaan Denys, The Netherlands; Enrico Domenici, Italy; Raul Gainetdinov, Italy; David Heal, United Kingdom; Erkki T. Isometsä, Finland, Mathias J. Koepp, United Kingdom; Frank R. Kooy, Belgium; Esa Korpi, Finland; Andrea L. Malizia, United Kingdom; James Nicoll, United Kingdom; Michael Ossipov, United States; Walter Pirker, Austria; Jill G.C. Rasmussen, United Kingdom; Mart Saarma, Finland; Trevor Sharp, United Kingdom; Guy Simonnet, France; Per Svenningsson, Sweden; Wim van den Brink, The Netherlands; Eduard Vieta, Spain; Veerle Visser – Vandewalle; The Netherlands; Helge Waal, Norway; William Wisden, United Kingdom.

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List of Abbreviations

| | |
|---|---|
| 5-HT | Serotonin |
| A2A | Adenosine type 2A (receptor) |
| Aβ42 | Amyloid beta 1-42 |
| AD | Alzheimer's disease |
| ADHD | Attention Deficit Hyperactivity Disorder |
| AED | Anti-epileptic drug |
| APOE | Apolipoprotein E |
| APP | Amyloid precursor protein |
| ASD | Autism Spectrum Disorder |
| AVV | Adeno-associated virus |
| BDNF | Brain-derived neurotrophic factor |
| BPD | Bipolar Disorder |
| CB | Cannabinoid |
| CDNF | Cerebral dopamine neurotrophic factor |
| CRH | Corticotropin-releasing hormone |
| D(1,2,3,4)R | Dopamine type (1,2,3,4) receptor |
| DA | Dopamine |
| DAag | Dopamine receptor agonists |
| DAT | Dopamine Transporter |
| DBS | Deep Brain Stimulation |
| EA | Extended Amygdala |
| FDA | Food and Drug Administration |
| GABA | Gamma Aminobutyric Acid |
| GDNF | Glia cell line-derived neurotrophic factor |
| Glu | Glutamate |
| GSK | Glycogen synthase kinase |
| GTP | Guanosine-5'-triphosphate |
| HPA | Hypothalamus-pituitary-adrenal |
| ITR | Inverted Terminal Repeat sequence in DNA |
| KO | Knockout (animal model with modified part of DNA) |
| L-DOPA | L-3,4-di-hydroxy-phenylalanine |
| MANF | Mesencephalic astrocyte-derived neurotrophic factor |
| MDD | Major Depressive Disorder |
| MPTP | 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine |
| MRI | Magnetic Resonance Imaging |
| mRNA | Messenger RNA |
| NA | Noradrenaline |
| NMDA | Glutamate N-methyl-D:-aspartate |
| NR(1,2) | Glutamate-binding NMDA receptor subunit NR (1,2) |
| OCD | Obsessive Compulsive Disorder |
| OIH | Opioid induced hyperalgesia |
| OPRM1 | Opioid receptor, mu 1 |
| PD | Parkinson's disease |
| PET | Positron Emission Tomography |
| P-gp | P-glycoprotein |
| PS | Presenilin |
| rAVV | Recombinant AVV |
| SSRI | Specific serotonin reuptake inhibitor |
| STAR*D | Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Study |
| STN | Subthalamic Nucleus |
| TCA | Tricyclic antidepressants |
| THC | Tetrahydrocannabinol |

Programme of the meeting can be found at the ECNP website:
http://www.ecnp.eu/about-ecnp/history/past-ecnp-meetings/past-stand-alone-meetings/~/media/Files/ecnp/history/stand%20alone%20meetings/ECNP_Meeting_programme.ashx]