Symposium

‘Emerging fields in mental health’

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Welcome

Dr. Marlies Dorlöchter, DLR-PT, NEURON Coordinator, Bonn, Germany

Marlies Dorlöchter introduced the scientific symposium on “Emerging Fields in Mental Health” by addressing a few welcoming words to the speakers and the NEURON Scientific Advisory board. She emphasized the need funding organizations have of such a meeting to understand what is important in the field of mental health and to shape future work. The ERA-NET NEURON is a European network of 27 funding organizations in the area of disease-related neurosciences, from 19 countries in Europe, Israel, Canada, and Turkey. Its purpose, as a network, is to improve interactions between the research community, policy makers, funding organizations and the general public, by discussing the main areas of interest in research and preparing joint activities, such as calls for research proposals.

NEURON aims to overcome issues such as bottlenecks of neurobiobanks, to improve the transfer of technology from bench to bedside, and to help promote interactions between scientists, clinicians, and the society as a whole. Moreover, one of NEURON's specific aims is to promote early career scientists by developing support measures.

NEURON’s priorities cover neurological, psychiatric and sensory organs' diseases, ranging from understanding disease mechanisms to disease progression and to preventive and interventional treatments. As a funding network for translational neurosciences, it seeks to have multidisciplinary projects and to combine animal research with patient research. NEURON is planning to launch in 2018 the third call about Mental Health, after 2010 and 2013.

Marlies Dorlöchter presented the outcomes of the projects of the Mental Disorders joint call of 2010. The funded research projects focused on the topics of depression, schizophrenia, autism, addiction and impulse control disorders, and on methods of imaging, genetics, epigenetics, and brain stimulation. The majority of successful consortia had collaborated before. While this is not surprising, the call also attracted new collaborations, funding by NEURON enabled therefore new exchanges of information, DNA, tissue samples, etc. From the point of view of translation, it appeared that more than 70% of the consortia were coordinated by clinicians, and 1/3 were carried out in clinical research labs or even hospitals. More than half of the projects performed both animal and human studies. This led to 190 publications, of which 50 were joint publications in high impact journals. Finally, some consortia went for direct application. They filed patents, founded a company, put databases openly accessible or developed software prototypes. Today's 2017's symposium places itself in this continuity, of improving international collaboration in neuroscience research in mental health.

Introduction

Dr. Etienne Hirsch (INSERM) and Dr. Bernard Poulain (CNRS), Paris, France

Etienne Hirsch and Bernard Poulain presented the general objectives of this symposium, whose purpose is to shape the next call which will focus on emerging fields in mental health. Mental heath disorders, as a major societal challenge in Europe, cost more than 800 billion euros; more than one third of Europeans experience mental health problems in any given year and even more will be affected indirectly. As such, not only it is a public health challenge, but also an economical one; costs in 2010 ranged to a sum of 461 billion euros and are presently still increasing, while, on the other

hand, funding for mental health remains extremely low. Thus, there is a dire need for more lobbying for research in mental health.

The general objectives of the symposium are:

- to review mental health priorities in Europe,
- to review the pertinent animal models,
- to discuss the impact of immuno-psychiatry disorders,
- to discuss new innovative treatments, both pharmacological and non-pharmacological
- to discuss the ecological monitoring
- and to discuss computational modelisation in psychiatry

Mental Health research priorities for Europe

Celso Arango, Gregorio Marañón General University Hospital, Madrid, Spain

In order to present the mental health priorities in Europe**,** Professor Arango shared the results of the ROAMER project, which was a coordinated and comprehensive roadmap in mental health and wellbeing research to promote and integrate the biological, clinical, social and public health aspects of mental health. It involved not only researchers but many different stakeholders, persons, societies, from the third sector, to academia, industry founders, etc. The project was founded by an FP7 3 year grant, from 2011 to 2014, and the main results have been published in the Lancet Psychiatry.

The relevant domains explored by the project were biomedical research and neurosciences, psychological therapies and treatments, social and economic aspects, public mental health, well-being, clinical research and integration (developmental and geographical), and finally infrastructures, funding and capacity building. They proceeded by analysing the state of the art (that is, what has been done in Europe, who is doing it, what centres, etc), to detect gaps and advances (taking in account what is done or not) and then priorities according to the following four criteria: i) efficacy / effectiveness, ii) impact / deliverability / economic benefits, iii) answerability / feasiblity and iv) European research strength (how good we are in trying to solve some of these gaps). The call precisely mentioned that Alzheimer disease and dementia should be excluded; all other ICD 10 nervous and mental health disorders were included. There was a large participation, with more than 600 researchers, in more than 250 associations, 30 policy makers and funders, and 9 industries. Participation was higher in the United Kingdom and Germany, after which came France, Spain, Italy and Northern Europe, but many other countries also from Eastern Europe participated.

The stakeholder advisory board included a great diversity of interests: patient associations, family associations, scientific associations. Interestingly, the ROAMER project received input also from experts outside of Europe, from Australia and the United States as well.

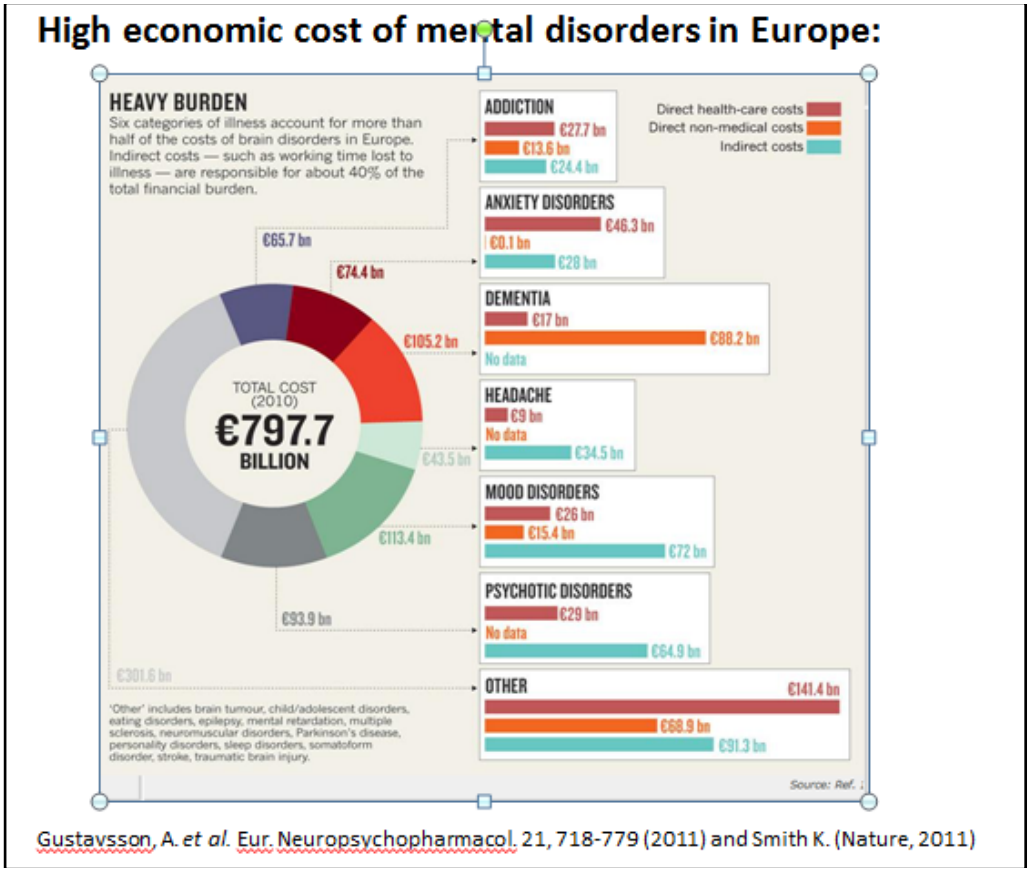
Current situation in Mental Health in Europe

Professor Arango presented examples of the results regarding the state of the art analysis: after systematic literature mapping they found for instance that the geographic distribution of publications in public mental health, weighted by the gross domestic product, is more important in the North than the South of Europe. There is a likewise distribution of randomized clinical trials-related publications, also weighted by gross domestic product. In terms of funding, there is a huge variance in what is allocated to research in mental health across different countries. The total amount allocated for mental health research in each country was compared to the percentage of health research budget allocated to mental health and the funding per capita for mental health research. So we see that for instance France allocates 4.1 percent of the health budget to mental health, compared to Finland which allocates 9.7, while at the same time the total amount allocated in

mental health research in France is eight times higher than in Finland. When looking at the distribution of European funding per country, one notes that the United-Kingdom and Germany receive most of the funds, followed by the Netherlands, and then Spain and Italy.

Establishing mental health priorities required: i) expert opinion / subjective methods, ii) valuing the burden of disease, iii) valuing the impact on patient clinical status / quality of life, iv) valuing the economic impact, v) a combination of criteria (including feasibility).

The challenge is tremendous as there is a discrepancy between the funding for research and disabilities caused by mental disorders, which are of great relevance. Not only do these represent 11.8 % of total disability-adjusted life years, compared to 17 and 17.7 % for cardiovascular and cancer respectively, but most importantly, unlike other areas of medicine, including neurology, this disability starts very early in life. The economic cost in Europe is high, even without taking Alzheimer and dementia into account: 692.5 thousand million euros per year.



Gustavsson, A. *et al.* Eur. Neuropsychopharmacol. 21, 718-779 (2011) and Smith K. (Nature, 2011)

Furthermore, a RAND Corporation study showed that the money invested in this area has a pay off, a return, that is not different from the pay off of other areas in medicine: for each euro invested by the taxpayer or charity donor in cardiovascular disease and mental health research, a stream of benefits is produced equivalent to earning respectively 0.39 and 0.37 euros per year in perpetuity. Professor Arango emphasizes the importance of this fact, especially to fight against the false belief funders might have that research in mental health doesn't pay off as much as other fields. When taking into account the funding strategies developed by the Framework Programme 7 (FP7), we see that only 4.9 % is invested in health, 0.7 % in ideas, and 0.8 % in people, which is a low percentage compared to the impact of disability in the population. There should be more research into preventive measures, resilience factors and buffer interventions for positive

mental health and well-being, as part of a wider focus: the necessity of integrating different levels of interventions is a specificity of our field.

Interestingly, the ROAMER report showed that Europe is very competitive, not only because of good scientists but also because of potentials and strengths not present in other countries, like the United States: less mobility of the citizens, stable health care systems that provide universal care in most of the countries, better ability of tracking individuals through healthcare, especially in countries of Northern Europe, which allows us to conduct studies that the competitors can't; and finally, health and welfare systems that differ across countries allowing natural experiments on these differences.

What are the high level priorities ?

Researchers, academia, industries, stakeholders, third sectors, patients and families, all have identified six main areas we should prioritize.

1_ ***Research into mental disorder prevention, mental heath promotion and other interventions in children, adolescents and young people.*** For example, we need to perform long-term prospective cohorts in order to study epigenetic risk and protective factors – the latter are not studied enough. Most importantly, we need to develop pharmacological and psychological treatments for children and adolescents. Although the FDA and EMA decided that, for every single drug that can be marketed in Europe, the industry is compelled to conduct clinical trials for children and adolescents, there is much investments in such studies as the indication of marketing will be give anyway. And the main problem is that many of the mental health disorders are neuro-developmental, so if we start giving drugs to adults, to person that have been ill for 30-40 years and have a phase 3 trial which is negative, we don't really know if these drugs could be affective in children, because probably the damage is already fixed and it's too late to see any difference. So it's not about conducting the trials in children and adolescents after they have been in adults, but starting proper trials in children and adolescents, while of course taking into account all the ethical issues. More than 70 % of all mental disorders start before the age of 24 and the outcomes are better if the care comes early.

2_ ***Focus on the development and causal mechanisms of mental health symptoms, syndromes and well-being across the lifespan (including older populations).*** For instance, we need to identify, as part of the RDoC strategy, what social and biological factors underlie risk or resilience factors for mental disorders and dimensions of observable behaviour and neurobiological measures across the lifespan. We should study how brain variations predict future mental disorder using longitudinal structural and functional neuroimaging.

3_ **Developing and maintaining international and interdisciplinary research networks and shared databases.** We could establish access to European mental health databases across different studies with standardized mental health outcomes.

4_ **Developing and implementing better interventions using new scientific and technological advances.** 50 % of all patients receiving pharmacological treatments do not respond at all to that treatment. There is a heterogeneity of how we define the disease and a necessity of identifying subpopulations that will benefit from treatment and biomarkers that predict treatment response. While for cardiovascular diseases, for instance, the different known mechanisms of actions went from 3-4 to 15-16, in depression however it barely went from 2 to 4, and for schizophrenia it's still at a standstill. So there is a real need of identifying patients with different pathophysiology that need different mechanisms of actions or different psychosocial interventions that tackle that pathophysiology.

5_ **Reducing stigma, empowering service users and carers in decisions about mental health.** We should study the role of stigma in the wider context of inequalities, and implement interventions to assess its place in public services.

6_ **Health and social systems research that address quality of care and take account of socio-cultural and socio-economic contexts and approaches.** For instance, one could do health-systems-level research on the cost-effectiveness of different ways of financing, regulating, organizing and providing services to promote and protect mental health.

What is there to be done ?

Professor Arango formulated the following requests:

As a researcher, one should pursue research informed by the roamer research priorities, aim to develop and expand interdisciplinary and international research networks, pool information with other researchers and institutions, and build opportunities for direct involvement of service users (and other stakeholders) in research.

As a policymaker, one should read and disseminate freely available ROAMER materials, work with researchers (and stakeholders such as service users) to produce truly evidence-based policymaking, build research into any new mental health policy, and ensure opportunities and funding for new research following the ROAMER priorities.

As service users, one should get involved in research, read and disseminate freely available ROAMER output, lobby policymakers to fund research into areas of service user interest and approach research institutions and funding bodies with you own research proposals

As a funding body, one should create funding calls based on the ROAMER priority areas, create more opportunities for interdisciplinary and international research projects – which is at the very core of the ERANET Neuron Project –, make the direct involvement of service users a requirement of funded mental health research projects and build continuations of funding into research, so that successful projects can immediately continue into implementation. One problem is that many of the interventions have only an effect in the long term so they can not be presented on a short term as politicians would like to.

Pertinent models

Nicoletta Berardi, University of Florence, Florence, Italy

To illustrate the recent changes in translational strategies, Professor Berardi discussed about research in the field of resilience. Resilience is the ability to cope with negative or traumatic events, to reorganize adaptively and to promote wellbeing in the face of adversities. By understanding what mechanisms underly resilience, we might find ways to promote it in vulnerable individuals and to design new interventions.

An example of a successful use of translation models for resilience is the area of aging and its associated frailties. On the one side, epidemiological and neuroscientific research data provided the rationale for the environmental enrichment approach – particularly useful during the prodromic and preclinical stages of pathological aging – identifying risk and protective factors which included being engaged in cognitively stimulating and social interactions, or practicing physical exercise. On the other, animal research provided the clarification of the essential components of this enriched environment; it described its effects on brain and behaviour: enhancement of neural plasticity, learning memory processes but also adaptability. This led to developing interventional studies, using cognitive or physical training and more recently a combination of both, finding positive effects on cognition (e.g, FINGER study, Ngandu et al., Lancet 2015; “Train the Brain”, Maffei et al, Sci Reports 2017); first on cognitively unimpaired elders and more recently on elders already showing cognitive deficits. As to the mechanisms of such interventions, both animal and human studies provided answers – for instance, relating factors such as BDNF or IGF-1 to plasticity, or studying the role of

neuro-inflammation.

There is therefore a virtuous spiral from epidemiological studies (risk and protective factors) and intervention studies in humans (validation) to animal studies for mechanisms (areas, circuits, neuronal type, molecule), to interventional studies in humans with assessment of mechanisms (validation), and back again to animal studies for further indications of therapeutical potential ("enviro-mimetics")... Could one apply the same frame of thought to mental health ?

Resilience in mental health: from GxE interactions to the differential-susceptibility model

The gene x environment (GxE) approach exploited in (Caspi et al, Science 2002, Science 2003) was the first to demonstrate that the effect of exposure to an environmental pathogen on a subject's health is conditional on its genotype. Many genetic variants, such a those for the 5-HT transporter, BDNF, CRHr1, COMT, DRD4 and FKBP51, have been found to moderate the relationship between various environmental stressors and various psychiatric and addiction problems. Use of longitudinal phenotypic data proved to be essential in order to confirm the validity of such GxE approaches.

The majority of G×E studies adhere to the diathesis (vulnerability)-stress model. However, this model has been criticized for disproportionately focusing on stressors and negative life events and showing less interest in positive environments. A differential susceptibility model has been proposed as an alternative (Belsky et al., Current Directions in Psychological Science, 2007). This model proposes that individuals vary in their susceptibility both to negative and positive environmental influences, rather than claiming that specific genotypes are inherently good or bad – one could therefore speak of "plasticity variants" (Halldorsdottir and Binder, Annu Rev Psychol., 2017).

Yet, the mechanisms of genetic resilience are still poorly understood, mainly because of a lack of pertinent animal models of GxE interactions – for indeed, most models are knock-out ones, which only allow us to look at effects related to the absence of the gene considered as a risk factor. On the contrary, a good model is for instance the one used by Soliman et al. Science 2010: after doing genetic editing on mice to make them express human polymorphisms, he demonstrated that the carriers of the genotype with a reduced BDNF action showed almost no response to extinction protocols. This was also found with humans, where neuro-imaging showed that this genotype was associated with a dysfunction in the emotional control brain circuit (decreased prefrontal cortex and increased amygdala activities), a dysfunction reminiscent of patients with anxiety disorder. Thus, a polymorphism such as the BDNF Val66Met might play a key role in the efficacy of treatments and may ultimately guide personalized medicine for related clinical disorders – it is noteworthy that a model that would have knocked-out the BDNF gene altogether could not have been used to reveal this mechanism.

Identification of epigenetic mechanisms: positive early environment and intermediate phenotypes

Epigenetic mechanisms have been identified as important effectors in psychiatric conditions.
They exert lasting control over gene expression without altering the genetic code. They are permissive or repressive regulators – respectively, histone acetylation versus histone and DNA methylation. More recently, non-coding RNAs such as microRNAs have emerged as a related mechanism – they control protein production so are not "epigenetic" per se. These are particularly attractive explanations, not only for how early life exposures to stress exert life-long effects on neuropsychiatric phenomena, but also for how positive early environments, such as maternal care (see Turecki and Meaney, Biol Psychiatry, 2016) or massage, have long lasting effects on anxiety-like behaviours, by affecting hippocampal glucocorticoid receptor (GR) expression, BDNF and IGF-1 (Hackman et al., 2011; Baldini et al., J Neurosc 2013). This affects the HPA stress response axis, making it physiologically activable but also physiologically quenchable leading to low levels of anxiety (Turecki and Meaney, Biol Psychiatry , 2016). Moreover, it is possible to eliminate negative effects of having

experienced low levels of maternal care, and their consequences on hippocampal GR expression and on HPA responses to stress, through drugs targeting epigenetic mechanisms, increasing hippocampal histone acetylation – for instance trichostatin A can selectively inhibit class I and II mammalian histone deacetylase enzymes.

The relation between adult stressful events and epigenetics has been particularly studied in mood disorders, one aspect of the disease being its long-lasting nature and delayed response to antidepressant treatment. This persistence was thought to be mediated by slowly developing but stable neural maladaptations, “molecular scars”, which might have included epigenetic regulation; but one had to wait for good animal models to start answering these questions. The development of such suitable animal models, with an environmental construct validity, helped clarify, for instance, the neural circuitry and maladaptive neuro-adaptations underlying aspects of depression (Bagot et al, Nature Comm 2015). Importantly, these models are based on the concept of intermediate phenotypes, proposing not a model for an illness, but for a more specific aspect of it, leading to an understanding of the circuit levels of anhedonia, sleep disorders, or impaired pattern separation for instance. They also have predictive validity as treatment courses are comparable to that required in humans

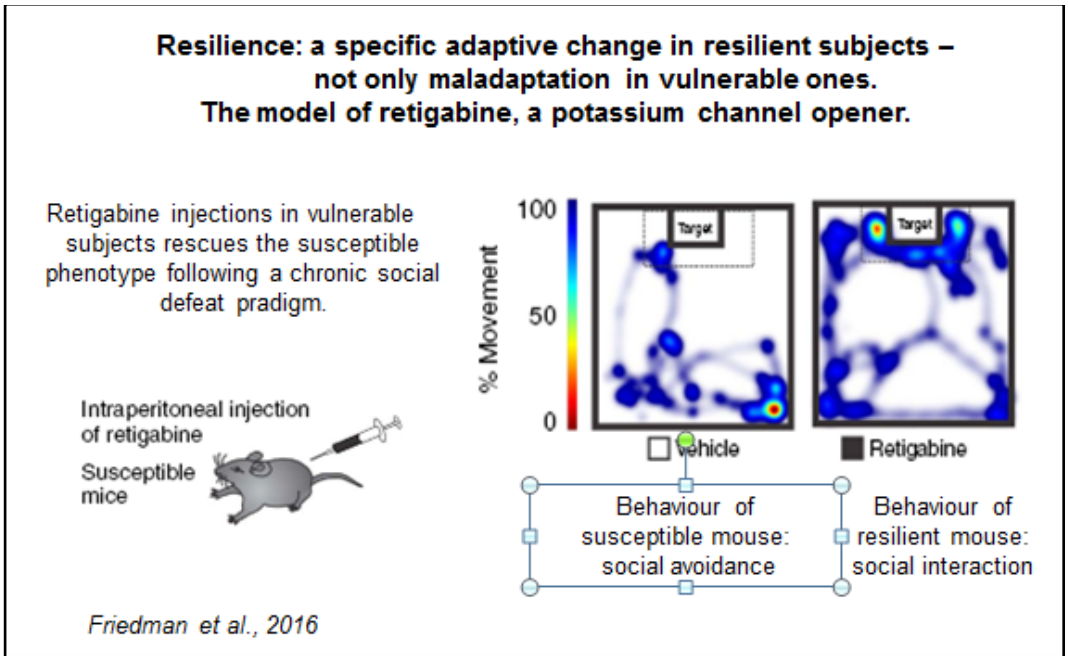
Professor Berardi gave as an example the chronic social defeat stress model, where a repeated social defeat and subordination is inflicted by a dominant male. On the base of the behavioural changes, defeated mice were segregated into those – susceptible – that displayed clear deficits in social interaction and those – resilient – that did not (Krishnan et al, Biol Psychiatry, 2008). And in susceptible mice, one found a decrease in the BDNF expression in the hippocampus via epigenetic mechanisms. These modifications were present four weeks after cessation of defeat stress and were only partially reversed by chronic, but not acute, antidepressant treatment, indicating that chronic stress imposes a long-lasting marker of repression at the BDNF promoters. As an example of the need we have to precisely understand the complex mechanisms of molecules such as BDNF, Professor Berardi also outlined the fact that in the ventral tegmental area (VTA) / nucleus accumbens (NAc) dopamine pathway, where BDNF is a key regulator at the basis of reward driven behaviour, chronic social stress leads to both its increase the NAc and decrease in the hippocampus.

One should keep in mind however, such chronic stress paradigms are sex-specific, as is the case of the epigenetic regulators themselves (Hodes et al., Nat Neurosci. 2015).

Resilience mechanisms as a source of treatments

The main idea underlying the development of treatments is that of “active resilience”, which is not only supported by a lack of maladaptive changes which take place in susceptible animals, but also by the presence of adaptive changes, taking place only in resilient subjects and which might be exploited to promote resilience in vulnerable subjects, both by treatment and by prevention. One example of such research is the discovery, in a social defeat paradigm, that resilient mice resist by upregulating several K^+ channels in the VTA, thus reducing the activity rate of VTA dopamine neurons, hence avoiding depression-like behaviours. Chaudhury et al., Nature 2013) showed that dampening VTA to NAc network activity, by over-expressing K^+ channels in the VTA, changes the mice phenotype from susceptible to resilient, both behaviourally and in terms of BDNF expression. A potential molecule of interest could be retigabine, a specific K^+ channels opener already used as an anticonvulsivant. It acts by increasing K^+ channels' action but not their number: its systemic administration normalizes the depressive phenotype (Friedman et al., Nat Commun 2016). Likewise, fluoxetine normalizes hyperactivity in VTA neurons. But interestingly, Friedman et al. (Science 2014) showed that in resilient mice, there was both an enhancement of excitatory activity, as well as a parallel increase in the K^+ channel-mediated control of the activity. As if the hyperactivity of VTA neurons were the driving force of a homeostatic plasticity that triggers the self-tuning response which increases potassium channels and brings back activity and behaviour towards physiological level. It is in this context that Alboni et al. (Mol Psychiatry. 2017) showed that depending on the environment, enriched or stressful, fluoxetine respectively reversed the chronic social

defeat phenotype or exacerbated the condition.



Professor Berardi gave another example of how translational research into resilience might lead to new treatments. A brain region, the dentate gyrus, was identified in rodents that mediates pattern separation – the ability to correctly contextualize a memory, which is necessary to associate fear to specific contexts, but also to extinct it when the setting is different. This triggered human investigations aimed at identifying patients with pattern separation deficits as well as dentate gyrus dysfunction. In turn, these patients became candidates for pharmacological interventions aimed at improving pattern separation, such as compounds that stimulate dentate gyrus neurogenesis (Donaldson and Hen, Transl Psychiatry 2016). But interestingly, a simple and potent stimulator of dentate gyrus neurogenesis and of hippocampal BDNF is physical exercise (see Sale et al., Front Behav Neurosci, 2015); physical exercise also potentiates cortical homeostatic plasticity (Lunghi and Sale, Curr Biol 2015)

Future topics of research

It is important to do longitudinal studies both in humans and animal models, to better understand active resilience and to maximize the probability of deriving therapeutic drugs (or treatments) from these studies. There is a necessity of better phenotyping human and animal models, while taking sex into account, and a necessity of moving beyond the single molecule hypothesis towards analysis of specific circuits altered in the disease and target active resilience. We also need better models for the mechanisms underlying genetic resilience/vulnerability.

Immuno-psychiatry disorders

Marion Leboyer, Université Paris-Est Creteil Val de Marne, Créteil, France

Opening new avenues for better understanding, diagnosis and treatment of major psychiatric disorders

It is in the context of major public health concern about the near standstill of innovation in psychiatric treatments that Professor Leboyer outlines what is needed both to bring back innovation and to raise the interest of the industry for drug discovery: 1) valid biomarkers for disease stratification, 2) reliable drug

targets, 3) pathways and pathophysiology, 4) endpoints for assessment and 5) animal models. Notably, all these criteria can be met in immuno-psychiatry, which most importantly demonstrates that psychiatric disorders are belonging to the field of medicine and can be treated as neurological or cardiovascular disorders are, for instance.

Marion Leboyer's presentation first sets the stage for inflammation in psychiatry, then discusses blood based biomarkers and describes the consequences of inflammation, to finally open on innovative treatments.

Setting the stage for inflammation

Inflammatory markers, pro-inflammatory cytokines, have been described throughout psychiatric fields: in depression, bipolar disorder, resistant depression; in schizophrenia, in schizophrenia with cognitive decline, in autism; but also in anxiety disorders, OCD, anorexia, suicide, etc. This trans-diagnostic inflammatory background can either be seen as an approach going beyond DSM categorizations, with certain dimensions underlying this inflammation, or as a subgroup of pathologies.

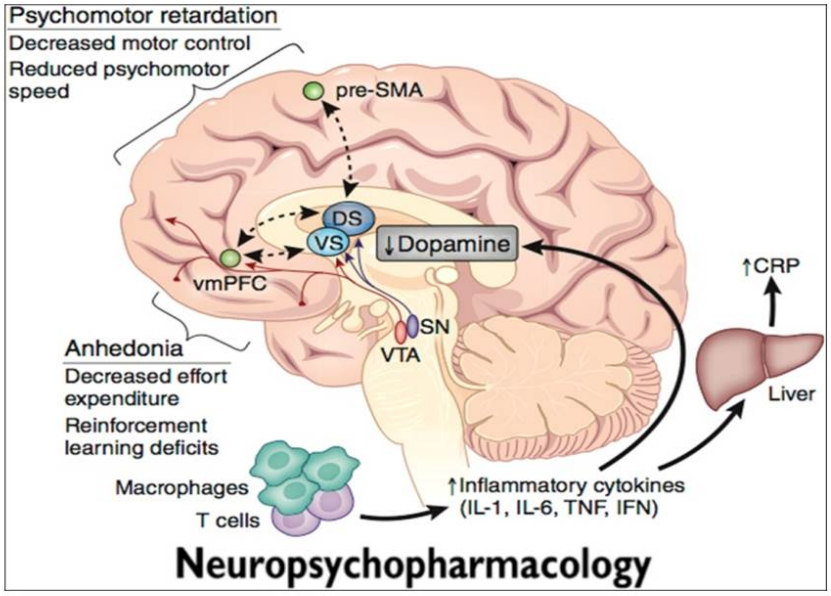
Interestingly, most patients have more than one psychiatric disorder and most of them present also with somatic comorbidities during the evolution of their psychiatric disorder – for instance, bipolar disorder is associated to autoimmune disorders, diabetes mellitus, cardiovascular disorder or obesity. And similar associations could also be found for schizophrenia or autism spectrum disorders. Such multi-systemic disorders are most likely explained by inflammation.

Furthermore, many studies have emphasized not only that various psychiatric disorders share the same genetic and environmental risk factors (Lichtenstein et al., in Lancet 2009, showed that bipolar disorders and schizophrenia were overlapping), but also that these risk factors had strong implications in immuno-inflammation. For instance, the GWAS study for schizophrenia-associated genetic loci, published by the Psychiatric Genomics Consortium in Nature in 2014, found a significantly positive signal in the middle of the region containing the HLA (Human Leukocyte Antigen) system, which has very strong implications in adaptive immunity, to control anti-infectious, auto-immune and pro-inflammatory responses. Likewise, inflammation is increased by environmental factors that have been shown to be associated with psychiatric disorders, such as infections or stress, occurring in specific windows – pre/perinatal life and childhood – or an unhealthy lifestyle, with sleep loss, unhealthy diet and low vitamin D, occurring throughout the life.

Blood-based biomarkers

The infectious stigma appears to be tremendously high in psychiatric disorders. As an example, influenza during pregnancy increases by a factor five the risk of bipolar disease. And simple urinary tract infections are nine times more frequent before an acute episode of affective psychosis. These are correlations much higher than those found between psychiatric diseases and genes such as neuregulin or DISC1, which have much smaller odd ratios. Northern Europe cohorts, like the Danish Birth Registry, were also able to demonstrate there is a three fold increase of autism spectrum disorders in children born to mothers hospitalized for viral infection or fever.

To understand why there can be such infectious stigma in some patients, who don't respond to environmental factors in the same way as others, one should take into account the diversity of the immunogenetic background. It influences the type and severity of infectious events, modulates the inflammatory response, and contributes to disorder severity and comorbidities. After the first phase of an infection, the genes encoding TOLL-like receptors react – they modulate innate response; then, the genes trigger the synthesis of chronic inflammation proteins and finally, in the second phase, 48h after the early infection, adaptive immunity sets off, governed by HLA. Each of these genes have been found to have genetic variants contributing to a low anti-infectious response, leading to persistent low grade inflammation. For



Felger et al., Neuropsychopharmacology, 2016

instance, it was demonstrated that in bipolar disorders, one can find in the blood peripheral markers of inflammation with elevated IL6, TNFα, and also elevated acute phase proteins with elevation of C Reactive Protein and also pro-inflammatory activation of the T-cell system and of the monocytes/macrophages system. In the CSF one found elevation of cytokines (IL1β) and also brain abnormalities of mRNA and microglia activation.

All these blood-based biomarkers are easy to access and the methods highly replicated and reliable. As an example, Professor Leboyer presented the European FP7 project "OPTIMISE", which followed 500 first episode psychosis and identified simple cytokines or HLA signatures, using machine learning, to predict with a high probability response to antipsychotic treatment.

Consequences of inflammation

Inflammation leads to increased permeability both at the blood-brain barrier but also at the guts barrier, leading to an increase in antigen trafficking and peripheral pro-inflammatory cytokines, and through this communication pathway to the brain, to endothelial and microglial activation, and production of brain pro-inflammatory cytokines. This alters neurotransmitters metabolism, increases oxidative stress and diminishes synaptic plasticity. Depending on the immunogenetic background, particularly the HLA, one can also develop auto-antibodies.

A good example of brain and peripheral auto-antibodies are the ones against the NMDA Receptor (NMDA-R), leading to a heterogenous neuropsychiatric clinical presentation, in the hours to weeks following a flu infection. Between 5 to 10 % of schizophrenic patients have the NMDA-R antibodies in the blood but Professor Leboyer and Laurent Groc from Bordeaux were able to demonstrate, using single particle tracking, that their mechanisms of action were very different between a full NMDA-R limbic encephalitis and a psychotic clinical presentation. In encephalitis, the antibody binds to a NMDAR's subunit, leading to its internalization and degradation thus dramatically reducing the glutamate system. In patients with psychosis, the antibodies change NMDAR dynamics at the synaptic cleft, producing a much broader movement. Hence different mechanisms might explain different phenotypes, and this is why it is important not only to diagnose patients, but also to understand the mechanisms, in order to find the adequate treatments. Immunomodulators and immunoglobulins totally cure these patients.

Another consequence of inflammation is the transactivation of Human Endogenous RetroViruses (HERV-W). These retroviruses, which are in 8% of the genome, are mostly inactive, but they can be reactivated by environmental triggers, such as infections, causing de novo genetic disorder, and leading to pro-inflammatory neurotoxic action and autoimmune disorders, and probably producing in some groups of patients a psychotic disorder.

Towards innovative treatments

The previously described mechanisms not only give us biomarkers to look for in order to improve

diagnosis (the envelope protein of the reactivated HERV can be found in the blood of patients and is highly correlated to inflammation markers like CRP), but it also gives new targets for new drugs. One could for instance try to inactivate the envelope protein causing the inflammatory response.

Professor Leboyer mentioned also the idea of drug repositioning, by citing a paper by Raison et al, in JAMA Psychiatry, 2013. It is the first example of precision medicine in the coming years. In a very severe disorder like resistant depression, the authors used as add-on an antagonist of TNFα, influximab. There wasn't any difference initially, but when the post-hoc analysis was made, a difference in effect was found between those who had a CRP lower than 5 mg/L, where influximab proved to be worse than placebo, and those with a CRP higher than 5 mg/L, where influximab proved to be more efficent than placebo.

Finally, the Professor Leboyer addressed the issue of developing better animal models. In autism, the maternal immune activation model relies on the induction of an infection during pregnancy, leading to autism related endophenotypes, characterized by behavioural abnomalities, including impaired social interaction, decreased communication, repetitive behaviour, abnormality sensorimotor gating and anxiety, all abnormalities having been found in patients with autism. And Hsiao et al (Cell 2013) tested the impact of probiotics to show that using this MIA model, the use of probiotics treats clearly not only the phenotype but also the abnormality at the gut level.

Future topics of research

In conclusion, Professor Leboyer summarized the important goals of the field: a more precise identification of patients' subgroups; valid biomarkers for stratification; new pathways that can be explored by using peripheral markers -not only infections but also inflammation, auto-antibodies, oxydative stress, microbiota, brain imaging. This, in the hope of going from the current nosology where highly heterogenous disorders are mixed to homogenous subgroups of patients, defined by a biological signature characterized by specific abnormal pathways. It could help to define a more personalized medicine base on stratified clinical trials.

Innovative treatments

Thomas Schlaepfer, University Hospital Freiburg, Freiburg, Germany

Innovative brain stimulation treatments find in depression an important and necessary field of application. Depression has a huge lifetime prevalence, a dramatic under-diagnosis and under-treatment related to its stigma, and high rates of mortality and somatic comorbidities. Most importantly, it is associated with the highest decrease in quality of life of all chronic disorders. Although most patients are treated by psychotherapy and psychopharmacology, 10 % develop treatment resistant forms. And despite electroconvulsive therapy, there still remains 8 % of patients who are even resistant to it.

A change in paradigms: the neuro-circuitry of mood as an example

The development of brain stimulation techniques is concomitant to the understanding of neuro-circuitry, of which mood is a good example. Berton and Nestler (Nat Rev Neurosci 2006) described these pathways, of both chemically and electrically communicating components, and associated the dysfunctions of specific parts of this network (previously identified by neuro-imaging) to symptoms of depression. Frontal cortical and hippocampal functions have to do with the cognitive aspects of depression (memory impairments, feelings of worthlessness, hopelessness, guilt, doom and suicidality); the hypothalamus has to do with neuro-vegetative symptoms (too much or too little sleep, appetite and energy, loss of interest in sex and other pleasurable activities); and the nucleus accumbens and the amygdala are implicated in mediating aversive and rewarding responses to emotional stimuli (anhedonia, anxiety and reduced motivation).

Such a model therefore raises the question of ways of modulating this network – that is, changing the function or dysfunction of part of the network, although there is little knowledge on how the stimulation methods precisely works. Furthermore, one should be aware that such studies involve very small numbers of subject, hence requiring great precautions in one's interpretations. With this caveat in mind, Professor Schlaepfer summarized the various techniques that exist.

Neuromodulation

Repetitive magnetic transcranial stimulation, as well as magnetic seizure therapy, can reach fronto-cortical aspects of the network. Vagus nerve stimulation uses the vagus nerve to reach the locus coeruleus, which has projections in the limbic system, hence ranging to different parts of the network (the method is very efficacious but encountered development issues related to the industry). Most importantly the deep brain stimulation allows neuromodulation in a reversible and very precise focus. A new form of neurostimulation is transcranial direct current stimulation (tDCS involves the use of a weak electric current passed through the brain tissue via electrodes placed on the scalp)- but with only few applications in psychiatry, although there is research to be done on potentially unexpected additional benefits of such treatments. Focused Ultrasound is also an interesting method using ultrasounds at levels allowing to at least temporarily destroy or impact tissue.

However, the deep brain stimulation seems to be the most interesting method at the moment: electrodes are connected subcutaneously to a stimulation device which in its function is exactly the same as a cardiac pacemaker - alternating current changes the function of certain areas in the brain. It is a method that has been widely used in neurology: more than 160 000 patients have been treated with deep brain stimulation for Parkinson associated movement disorders. And this method has entered psychiatry about a decade ago, in the field of OCD and depression. For the latter, several targets were proposed: the subcallosal cingulate (SCC), the anterior limb of the capsula interna (ALIC) and the nucleus accumbens (Nacc).

Early results showed a decrease of the Hamilton and MADRS scores under stimulation of the SCC (Lozano, Biol Psychiatry 2008) and the ALIC (Malone, Biol Psychiatry 2009). And despite the small number of patients in the groups, there was a significant decrease of depressivity under stimulation, within a month.

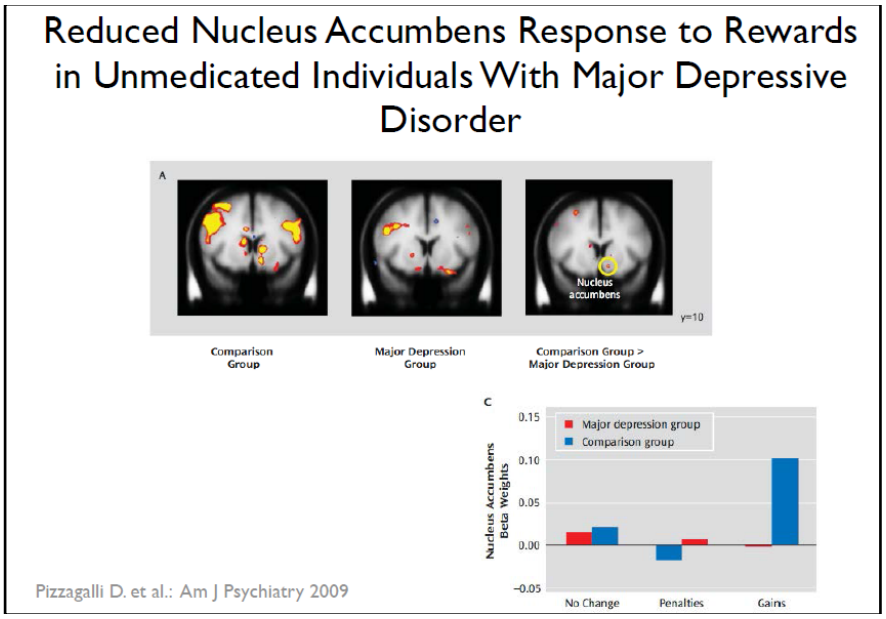
The issue of industry designed studies

Although more studies like the previous have been done with success, the only slightly larger trials (30 patients in the “RECLAIM” study) were designed by industry and didn't show any difference in efficacy compared to placebo. Patients had been implanted and implantation led to a small decrease of depressivity. Then they were randomized and they had a slight antidepressant effect, but after week sixteen the sham treated patients had a better effect than those who were treated. Moreover, the placebo control was perfectly respected since patients can not feel the stimulation. This is why the first larger randomized controlled study led to a lot of demise in the field of deep brain stimulation. However, there are many critiques to be made to it: the short observational period (4 months is meaningless in the course of treatment resistant depression), the huge center effects, the parameter settings that were not manualized so that it wasn't clear whether patients had been treated at real antidepressant levels, etc. This is the reason why Professor Schlaepfer strongly advocates against study designs by the industry, which might have different interests than researchers in the field.

Current research with deep brain stimulation in anhedonia

Since anhedonia (inability to experience pleasure in situations that were previously pleasurable) is the most important symptom in depression, it appeared to be a good target. Major depression is associated with dysfunctions in a system that relays hedonic stimuli, the reward system. Pizzagalli et al Am J Psychiaty 2009) clearly demonstrated this by looking at BOLD signals showing that there is almost no variation of activation in

the nucleus accumbens in depressed patients compared to controls when winning or losing money.



The reward system consists of the ventral tegmental area, which projects dopaminergically by the medial forebrain bundle to the nucleus accumbens, which in turn acts as a relay structure, if the stimulation is high enough, to activate the pre-frontal cortex. In depressed patients, Bettina Bewernick and Thomas Schlaepfer (Biological Psychiatry, 2010) did the first study that used deep brain stimulation of the nucleus accumbens. Importantly, responders not only had a statistically and clinically significant decrease of the depression score on the Hamilton scale (more than 50%), but the effect was maintained as long as the stimulation was, hence refuting the placebo effect, which has efficacy in depression, but not in a time longer than three months.

Nevertheless, response outcomes in the three different target sites explored so far were between 50 and 60 %, while the baseline depression severity was the same and there was a similar effect size (high stimulation tensions are used, 10 volts, versus 3-4 in Parkinson). Therefore one tried to find a way to improve efficacy by recruiting a higher number of fibers, and a diffusion tensor imaging study was done: it showed that all targets were in the periphery of the medial forebrain bundle; a structure very important in all vertebrates to mediate activation and hedonic behavior. Hence DBS, with its three initial targets, was only stimulating a small peripheral amount of fibers. This is why Schlaepfer et al (Biol Psy, 2013) tested the hypothesis of taking the DBS deeper and closer to the ventral tegmental area, to get a higher proportion of fibers, for a higher anti-depressant effect. Although it was done on a small number of patients (8), the effects were both rapid and pronounced, with a mean decrease of baseline depressivity by 80 % on the MADRS scale. On a longer term outcome, it appeared that all of the 30 patients treated so far not only showed the same immediate effect, but also maintained their improvement on the MADRS score for 4 years, which in psychiatry is amazing, as many therapies cease to be affective after a while. This was confirmed in a placebo controlled double-blind study, with a randomized allocation to immediate switch on versus delayed activation. Moreover, there are no stimulation related side effects and the median intensity of 2.8 mA is about 30% of the one used in previous studies, proving site specificity. Also, no change in measures of personality was found when comparing profiles (conscientiousness, agreeableness, openness to experience, extraversion, neuroticism) at baseline and after six months.

In conclusion, this appears to be a system that allows patients to process reward associated-stimuli in a normal way, leading to rapid and sustained anti-depressant effect. At the moment, a third study with a higher

number of patients is planned.

Future topics of research

The “closed loop stimulation” has been looked at for epilepsy in the last years: one monitors the local field potentials, the local electrophysiological environment and a computer decides whether to stimulate or not. It might be interesting in depression because one probably can record prefrontal electrophysiological symptoms – which give information on what's going on really deep in the reward system – and then have an affect decoding controller, which looks at what happens at affect related stimuli and can do a stimulation if needed. Professor Schlaepfer's team just started a project where they looked whether there are really distinct clear electrophysiological changes, with the idea of personalized medicine in mind, as different patients might do different depressions, and this need different approaches.

More generally, there is a need for excellently designed, unbiased clinical trials (although funding is extremely hard to obtain), comprehensive neuroethical studies in order to decrease stigma, both for the disorder and the treatment, and comprehensive studies on modes of actions (imaging, microdialysis, electrophysiological...).

Ecological monitoring

Philippe Delespaul, Maastricht University, Maastricht, The Netherlands

Although the global burden of disease seems to improve, it is mainly due to advances in somatic health: the challenges faced by psychiatric health are still enormous and they require the same long term ambitious targets as there are for global warming, child death or other sustainable developmental goals. It could include reducing psychiatric morbidity, suicides and severe mental illness by a third, increasing social participation by a third and reducing the life expectancy gap by 50% (which reaches almost 25 years, mainly due to somatic diseases not diagnosed).

Yet, our diagnostic system, be it the DSM or the psychometric dimensional one, is set on making predictions on individual patients, based on a group reference, as found in the literature. This leads to a reduction in information and difficulties in gaining in science knowledge and optimizing treatment for a specific person. However, improving our “member” validity approach by making more fine grain assessments doesn't appear to be the best option. For instance, despite the knowledge that schizophrenia is a heterogenous disease and the great increase in diagnosis sophistication, it didn't lead to better interventions at the moment. Moreover, even if it were possible, the information might very well be to big to allow us to gather it in the purpose of specifying subgroups. Professor Delespaul therefore calls for a rethink of how we frame our field and develop our knowledge base.

The challenges of clinical assessment and interventions

The notion one has of psychopathology is that it's neither an identity, nor an etiology, but it is contextualized, as a result of a gene x environment interaction. This is however, only a heuristic concept, and it is difficult to disentangle the processes related to these interactions. But if one sees psychopathology as a vulnerability that becomes periodically problematic over time, as something that doesn't always lead to a determinist cause but is often periodic or recursive, one could focus on helping people to develop resilience in context. That is, from a clinical and social point of view, not necessarily focusing only on “fixing the illness” (since the strategies one develops in clinical practice often lead to another iatrogenic illness), but more importantly helping people in their environment to become more resilient in front of the problems they encounter. It implies looking simultaneously at different domains of recovery, which are all linked: the recovery related to symptomatology is the one we focus a lot on already; but there is also recovery related to

social integration and the recovery related to personal life meaning, purpose of life.

This is why, one needs a better assessment that relates to each person / environment interaction, a dynamic process of understanding how people can function. Ecological psychology sees “behaviour” as a function of “person” and “environment”, where the concept of “behaviour” encompasses also cognition, emotion and perceptions, and “person” includes information on genes, learning history, traumatic events, etc. But the challenge is that the issues most relevant in a mental health field, such as cognition, emotion and perception are not of public access like behaviour or context. And when people are asked retrospectively about these dimensions, it's difficult for them to describe precisely what happened to them, how they experienced pain or depression, for instance.

Thus there is a need for more reliable assessments of subjective experiences (this means no independent assessment), in daily life, taking account of contextualized variations. And treatment should do with understanding the triggers of vulnerability and of recovery. Accordingly, one needs interventions that are portable (“therapist in the pocket”): not only drug treatments, but also skills that one learns in psychotherapy . Professor Delespaul also points out that one should developways to customize treatment strategies, to understand what helps, for whom, in which kind of circumstances and to be able to adapt these strategies. The aim is to increase resilience in a way that people become autonomous, therefore one needs a transparent communication on diagnosis, one that can be understood by patients. Finally, one needs more ways to engage people in care. For all these reasons, according to Professor Delespaul, “mHealth” (mobile Health) appears to be one way to move in that direction. It means embedded assessment in daily life for embedded care.

The experience sampling method (ESM)

The ESM assesses how people feel from moment to moment in daily life, in a dynamic process of making snapshots of context and snapshots of mental states, thus creating a film of daily life with the following characteristics: an assessment that occurs ten times a day, for a week or more, with a critical mass of moments to understand when vulnerability or resilience occur, using questionnaires that assess 25-35 items ten times a day and that don't last more than one minute and a half - it is a very small intervention signaled by a bip. Years ago, the ESM was done by paper and pencil work and it was almost impossible to implement this in a normal clinical practice. But now, these data collections can be automatized and done by apps such as the PsyMate App.

The ecological assessment strategies are very diverse: event sampling, time sampling, continuous monitoring, sensor harvesting. These are “families of methods” and not a standard questionnaire. It's a random sampling, so that people can go on with their daily life, and avoid an anticipation that otherwise would interfere with their life. Also, the questions asked are open, there isn't a standard questionnaire, we can assess emotion, cognition, behaviour, perception and context. The collection methods are diverse and the purpose could either be assessment (for contextualized dynamics) or intervention (for mobile therapy).

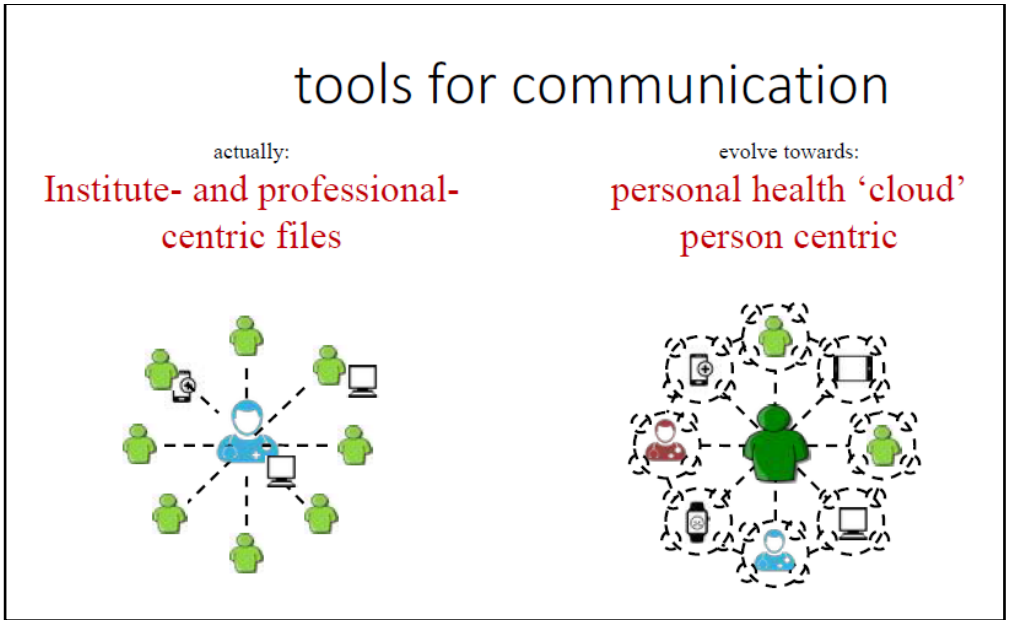
Implementing (optimized) care: the aim of future research

Whether one looks at resilience from the symptoms' point of view, or their ability to participate to daily life, or subjective personal recovery, collaborative care is needed – that is, not only care that comes from the professional but care which is integrated in the lives of people. Importantly, an intervention that doesn't work today might still work next year. So making decisions on non response is not always a good thing to do. This is why, instead of looking for an optimal complicated algorithm to improve the strategy, it can be done in a dynamic way. To approach such a dynamic optimization, the collaborative process between patient and clinician requires a language where the patient is in charge of the information as well as the clinician. So mystifying that with diagnostics that are not related to their daily life experience is often creating a burden in this kind of communication.

As an example of the collaborative strategies he is working on, Professor Delespaul spoke about optimization of medication titration and tapering, which is allowed by such interactions in an iterative process; for indeed, people have antidepressants or antipsychotics for too long a time and too high a dose.

In this context, the data has to belong to the client and not to be professional-centric anymore. Because, if clients become resilient, move away from clinical situations and still become paranoid or anxious again, they should be able to activate this technology to understand their dynamics in daily life without having a clinician present. And they should be able to share these informations with important people in their network, that can help them out coaching this kind of decision process.

Improving the continual assessment is also an important challenge.. Although collecting data ten times a day provides a rich data set, it is still an under-sampling of the richness of people's daily life, and we miss part of the dynamics' continuity of some diseases. Of course, it's impossible to assess mental states in a continuous perspective without asking people, but it's possible to generate systems where we increment the self-reported data with continual data and build an understanding of the combination of both. As an example, although people can be tracked by GPS, from a clinical point of view, one has to know whether it's a meaningful location or not (at home, at work, with friends). If the continual assessment GPS location is combined with the labelled assessment of the subjects' self-report, one gets a rich coding system that's dynamically built and that gives us better information on the flow of daily life. Finally, there is a need of integrating the information of the group into the information of the individual, by having data that people don't have to write down ten times a day. And building a feedback system will improve collaborative care and optimize our treatment for the next three to five years.



Delespaul,2017

Computational modelisation

Robb Rutledge, University College of London, London, UK

Computational psychiatry is the idea that we can use mathematical tools to understand and to treat mental illness. There are two major approaches: the data-driven approach, which applies machine learning techniques on large neuro-imaging data sets to try to pull patterns out of the data; and the theory-driven approach, which develops computational models for specific mental processes and then test their relevance for understanding and treating diseases. The latter approach is used by Robb Rutledge's lab at University

College London to study mood disorders, including major depression and bipolar disorder, and to address several major questions of the field: i) Can computational models bridge the gap between neurobiology and subjective psychiatric symptoms with models of subjective states like mood? ii) Can novel tasks and models produce computational markers for psychiatric disorders and for guiding personalized treatment? iii) Once there are good models for disorder-relevant neural circuits, can computational models bridge across levels (genetic, neural circuits, cognitive, social, and environmental)?

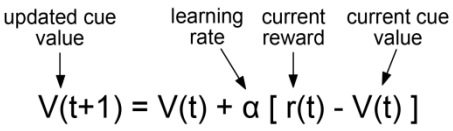
The relevance of this research for depression, for instance, is great, as more than 350 million worldwide suffer from it. Since diagnosis is largely based on subjective symptoms that in some way relate to happiness (depressed mood, anhedonia, guilt/worthlessness/helplessness, suicidality), and happiness has been closely linked to reward, Robb Rutledge has asked whether computational models of happiness may be useful for understanding the symptoms of depression. It seems indeed that many of depression's symptoms might relate to a low expectation of future reward.

Modelisation of happiness: linking dopamine and reward prediction errors

In the popular value-based decision-making framework, we compare the outcome of a decision relative to what was expected, a 'reward prediction error' (RPE). RPEs can be used to learn about the environment and to improve the value estimates associated with possible choices. This well-studied framework in neuroscience does not account, however, for emotions. We don't know for instance whether we actually feel RPEs. This is why subjective self-reports, which are used by clinicians to evaluate patients and to make diagnoses, are also very important for this field of research.

To describe the RPE from a neurophysiological point of view, Robb Rutledge gave the example of a study where dopamine neuron activity was recorded in the brain of awake monkeys (Schultz, Dayan & Montague, Science 1997). When monkeys got an unexpected reward, there was a burst of dopamine activity right after it. This would be a positive RPE. Then, after the monkey was taught to associate a cue – a tone – with the reward received a second later, the dopamine activity moved to the time of the cue. In this case, at the time of the fully anticipated reward, there was no change in the dopamine activity, that is, a null RPE. Finally, if the expected reward was omitted, the dopamine neurons decreased their activity in response to this negative RPE.

Mathematically, the standard reinforcement learning models based on RPE include a value update term that looks like this:

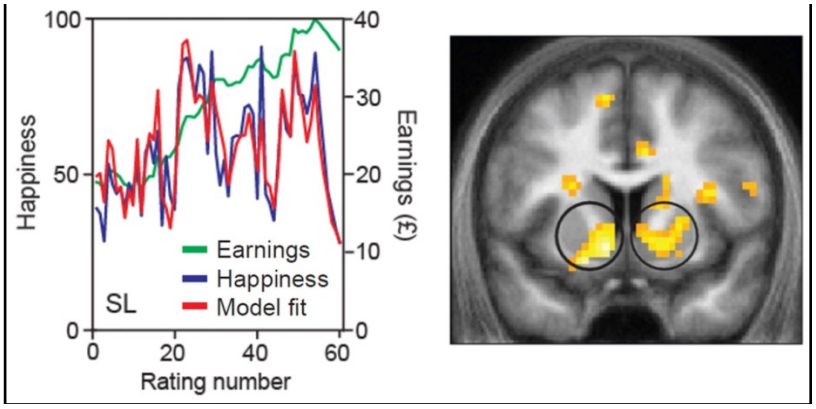


The value V(t) for a cue, which is initially not associated with a reward, would be updated on each trial by the RPE times a learning rate. The learning rate determines how fast we learn about the environment. This is a simple but very powerful concept because it means that we can learn from experience and over time our value estimates should get closer to the true values of options in the world. The value of options can change over time but such a mechanism allows us to keep adjusting our value estimates based on feedback and allows us to make better and better decisions.

$$Happiness(t) = w_0 + w_1 \sum_{j=1}^{t} \gamma^{t-j} CR_j + w_2 \sum_{j=1}^{t} \gamma^{t-j} EV_j + w_3 \sum_{j=1}^{t} \gamma^{t-j} RPE_j$$

In order to account for emotions, Rutledge et al. (PNAS, 2014) designed a trial where subjects started with £20 and had to make a choice between a safe option (£0) and a risky one (flipping a coin to win 65p or lose 36p). After every two or three trials, they were asked to answer "how happy are you at this moment?" by moving a cursor on a line indicating their current subjective state. It appeared that the curve indicating the subjects' earnings, which was increasing over the course of the experiment, was not closely related to the curve representing the course of their happiness ratings, which varied quite a lot during the experiment. To propose an equation that would predict changes in happiness over time, the authors used parameters linked to the previous understanding of the neurobiology of reward. At the time of the outcome, it is possible to measure the RPE signal broadcasted through the brain by dopamine neurons; also, at the time the subjects make choices, one can measure dopamine-related signals that represent the expected value (EV) of chosen gambles and the value of the safe options with certain reward (CR) that they sometimes choose instead. This led to the following equation, where we ask whether happiness is a recency-weighted average of past certain rewards, the expected value of chosen gambles and the reward prediction errors experienced as the result of those gambles. The γ parameter determines the rate of decay – how fast subjects forget about previous events.

When fitting the model to the data, it appeared that it could well account for the variance in happiness over time. On average, happiness depended not on how well subjects were doing in the task, but on whether they were doing better than expected. The authors looked also at the parameter estimates they got from the model and found that all three – certain reward, expected value and reward prediction error – were positively correlated with happiness. Furthermore, the data was confirmed by BOLD activity in the striatum that correlated with future happiness ratings. Doing the experiment while being scanned in an MRI machine revealed that the brain activity in the ventral striatum – an area that receives a lot of input from the dopamine neurons – can be used to predict changes in happiness.



Rutledge et al 2014, PNAS

Also, this model was replicated on a much greater scale with the "Great Brain Experiment", an app that can be downloaded for iPhones and Android (www.thegreatbrainexperiment.com), and includes eight different games based on cognitive research at UCL. Some of the games focus on working memory, impulsivity, visual perception, and happiness with a similar design to the experiment previously described. This allowed the researchers to see the same pattern in 18,420 subjects, that were in completely different environments, with no instructions, no particular incentives to tell the truth, and still the same equation could account for mood dynamics, thus also confirming the potential of using smartphones to investigate complex subjective and unstable concepts such as happiness.

Such a framework of thought is highly applicable to psychiatric disorders. Rutledge et al. all showed that subjects who used the app and reported depression showed the same movements in happiness, depending on the same parameters (JAMA Psychiatry, 2017). And when we account for all the dynamics over the course of the game, we are left with a baseline parameter in the model that is highly correlated with severity of symptoms as reported using a BDI depression questionnaire. Thus, such a smartphone approach seems to reflect something about the overall mood that goes beyond the environment of the game and could be used to longitudinally assess patients over time, to see how their performance in the games relates to experience sampling measures or symptoms collected by clinicians, for instance.

How is decision-making related to psychiatric disorders?

Robb Rutledge began this second part of the speech stressing the fact that despite recent results linking psychiatric disorders to deficits in learning, there is still much to be done on the level of decision-making, as this is the main outcome of learning. Gillian and Daw showed for instance that goal-directed learning was impaired by a dimension related to compulsive behaviour but not a dimension related to anxiety-depression (eLife, 2016). Browning et al. demonstrated that anxiety impaired learning in high uncertainty environments (Nature Neuroscience, 2015). It also appeared that by using a hierarchical Bayesian learning model, it is possible to quantify the relationship between the different forms of subjective task uncertainty and acute stress response (de Berker et al., Nature Communications, 2016).

But what about the impact on decision-making? Using for instance gain-only trials, where subjects have to choose between certain gain and a gain gamble with a larger potential gain or zero, it has been shown that anxiety increases the degree of risk aversion but not loss aversion (Charpentier et al., Biological Psychiatry, 2017). Furthermore, Rutledge et al. used a combination of neuroscience experiments and large scale data to show that there is a particular parameter in a new decision-making model that related to the neurotransmitter dopamine (Rutledge, Skandali, Dayan & Dolan, J Neurosci, 2015). They administered either placebo or 150 mg of L-DOPA to boost dopamine levels in 30 healthy subjects before performing an economic decision-making task, and they saw a dopamine dose-dependent increase in risk-taking behaviour (since subjects with the same dopamine dose had different body weights leading to different blood dosages). The authors then studied the effect on dopamine on the risk aversion parameter, as classically described in the “Prospect Theory” model from economics. Prospect Theory states that the propensity to choose risky options depends on the value of available options. So it was expected that the greater the expected reward would be, the more the risk aversion parameter would increase when subjects take L-DOPA compared to placebo. This, however, was not the case, so the authors developed another model, “The parametric approach-avoidance model”, with a new parameter, β gain, which acts as a value-independent influence on the probability of choosing the option with the largest potential gain.

$$P_{gamble} = \frac{(1-\beta_{gain})}{1+e^{\mu(U_{gamble}-U_{certain})}} + \beta_{gain}$$

For trials containing gambles with potential gains but not potential losses, β gain was significantly greater under L-DOPA than placebo. One possible interpretation of the valence-dependent but value-independent terms in the model is that they represent forms of Pavlovian approach in the face of potential gains. A similar parameter applies also in the domain of losses. Such Pavlovian influences are elicited without regard to their actual contingent benefits. Additionally, L-DOPA boosted the increase in happiness that followed small rewards, outcomes that on placebo increased happiness by only a small amount. These results are consistent with an association between dopaminergic RPEs and incentive salience, which can, in principle, provide an account of dopaminergic drug effects on pathological gambling and impulsive behaviour.

Again, such knowledge can be used on a greater scale, for instance in the study of the effect of age on risk taking. We know there is a progressive decline in dopamine over the course of the lifespan, and we can ask the question whether this has an effect on the choices people make. Indeed, on a group of 24,706 people who used the smartphone app, it appeared that this β parameter decreased steadily with age, showing less

willingness to take gambles for potential rewards (Rutledge et al., Current Biology, 2016). Interestingly, there was no increase in loss aversion with age.

Future topics of research

This well-established framework of value-based decision making is now being tested in many psychiatric populations but it is still very early days for research in computational psychiatry. In the future, we will need to study patients longitudinally to see if parameters from the computational models can predict clinical outcomes, and can also be combined with neuro-imaging data. Now that there are large psychiatric neuro-imaging datasets (with, for example, structural connectivity measures and DTI measures), there is a need for stratification into clusters based on models of behaviour and emotion. Thus computational models can provide information that reflects the state of the neural circuits that underlie symptoms and will be useful for deciding what therapy would be most effective for an individual.

Annex I

List of participants

Speakers at the scientific workshop "Emerging fields in mental health"

1. **Celso Arango,** Gregorio Marañón General University Hospital, Madrid, Spain
2. **Nicoletta Berardi,** University of Florence, Florence, Italy
3. **Marion Leboyer**, Université Paris-Est Creteil Val de Marne, Paris, France
4. **Thomas Schlaepfer,** University Hospital Freiburg, Germany
5. **Philippe Delespaul,** Maastricht University, Maastricht, The Netherlands
6. **Robb Rutledge,** University College of London, London, UK

NEURON SAB members and other Pannelists

1. Paola Bovolenta, Madrid, Spain
2. Silvana Galderisi, University of Campania Luigi Vanvitelli, Italy
3. Josep Maria Haro, Saint John of God Health Park, Barcelona, Spain
4. Chapman Joab, Tel Aviv, Israel
5. Jean-Antoine Girault , Paris, France
6. Elizabeth Kuipers, London, UK
7. Luc Mallet, Paris, France
8. Raluca Nica, GAMIAN-Europe, Romania
9. Fabrizio Tagliavini, Milan, Italy
10. Frauke Zipp, Mainz, Germany

Guests

1. Niall Boyce, Editor of The Lancet Psychiatry
2. Cule Cucic, ZonMw, The Netherlands
3. Mark Goldammer, Scientific officer, European Commission
4. Anton Iftimovici, Psychiatry Resident, Paris Descartes University, France
5. Frans Zitman, Mental Health board, The Netherlands

NEURON Partners

1. Ignacio Baanante, ISCIII, Spain
2. Jan Barancik, SAS, Slovakia
3. Ana Barra. MINECO, Spain
4. Uldis Berkis, VIAA, Latvia
5. Recep Emrah Cevic, TÜBITAK, Turkey
6. Mercedes Costi, MINECO, Spain
7. Anne-Cécile Desfaits, FRQS, Canada-Québec
8. Marlies Dorlöchter, DLR-PT, Germany
9. Maria Druet, ICSIII, Spain
10. Juan Jose Garrido, MINECO, Spain
11. Nathalie Gendron, CIHR, Canada
12. Anna Gossen, DLR-PT, Germany
13. Rob Heinsbroek, NWO, The Netherlands
14. Etienne Hirsch, INSERM, France
15. Cinzia Kutschera, MOH, Italy
16. Mihaela Manole, UEFISCDI, Romania
17. Hannele Lahtinen, AKA, Finland
18. Herbert Mayer, FWF, Austria
19. Sheyla Mejia, ANR; France
20. Melanie Neijts, NWO, The Netherlands

21. Rachael Panizzo, MRC, UK
22. Bernard Poulain, CNRS, France
23. Erkki Raulo, AKA, Finland
24. Raffaele Ruocco, MOH, Italy
25. Christine Tuffereau, INSERM, France
26. Laura Valstar, The Brain Foundation, The Netherlands
27. Ayelet Zamir, CSO-MOH, Israel