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Foresight Symposium 2022
“Mechanisms of Resilience and
Susceptibility in Mental Health”

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Report written by Frédérique SUEUR

Inserm, France

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“Outreach and interaction activities”

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Tables of Contents:

Welcome	4
Dr. Marlies Dorlöchter (Switzerland)	
Introduction	5
Dr. Etienne Hirsch (Paris, France) and Dr. Bernard Poulain (Strasbourg, France)	
Common factors in vulnerability and resilience in mental health: General psychiatry & focus on addiction and eating disorders	6
Pr. Chantal Martin-Soelch (Switzerland)	
How is the interaction between the environment and mental illness mediated in the brain?	9
Pr. Andreas Meyer-Lindenberg (Germany)	
Early interaction and bounding	11
Pr. Ruth Feldman (Israel)	
Role of metacognition in protection, resilience and vulnerability to mental disorders	14
Pr. Francesca Maria Bosco (Italy)	
Post-traumatic stress disorder and resilience	15
Dr. Pierre Gagnepain (France)	
Role of immune system in resilience and susceptibility in mental disorders	19
Pr. Marion Leboyer	
Increase resilience through new technologies, new therapies and new patient care	25
Pr. Giuseppe Riva	
Panel discussion with representatives of European patient organizations.....	28
Peter Kinderman (MHE) and Raluca Nica (Gamian Europe)	
Annex	283

Foresight symposium 2022

Welcome

Dr. Marlies Dorlöchter, DLR-PT - NEURON coordinator (Germany)

Marlies Dorlöchter, as coordinator of ERA-NET NEURON, introduced this Foresight symposium on “Mechanisms of Resilience and Susceptibility in Mental Health” by welcome addressing all attendants: scientific speakers, representatives of patient organizations, members of the NEURON Scientific Advisory Board, researchers from Estonia, Latvia, Slovakia, Taiwan and Turkey, representatives of NEURON partner organizations, and early career researchers. She highlighted for funding organizations the two main aims of this meeting: (i) to provide an expert overview on “Mechanisms of Resilience and Susceptibility in Mental Health”, and (ii) to shape the planned Joint Translational Call (JTC) for proposals in this area.

ERA-NET are networks of funding agencies and ministries, in Europe and beyond, getting support from the European Commission. NEURON (Network of European funding for Neuroscience research) is an ERA-NET in the area of brain research. Starting in 2003 with four funding organizations, it developed constantly and now comprises 26 funding organizations with partners well beyond Europe such as Canada and Taiwan. One of the key elements of NEURON is launching JTCs for research proposals, because multilateral, interdisciplinary innovative research is key to explore the brain and its diseases, and to help finding therapies and diagnosis tools for various disorders. A special feature of NEURON are the calls for proposals for research projects on Ethical, Legal, and Social Aspects (ELSA) of Neuroscience, a unique international funding instrument. NEURON’s purpose as a network is not only to promote brain research, but also to improve interactions between the research community, policy makers, funding organizations and the general public. In discussions with European and national policy makers, NEURON strives to gain enhanced consideration for brain research. It also interacts with the research community in various formats such as foresight symposia, workshops, newsletters and journal editorials. NEURON also includes programs to support early-career researchers such as inviting them to networking activities and FENS conferences as well as the Excellent Paper in Neuroscience Award.

The topic of “Mechanisms of Resilience and Susceptibility in Mental Health” emerged from the 2020 update of the NEURON Strategic Research Agenda. The call for proposal will fund research collaborations in this domain of research, between teams from NEURON countries. This Foresight symposium will allow defining precisely the scope of this call for proposal.

Introduction

Dr. Etienne Hirsch, INSERM (France)

Dr. Bernard Poulain, CNRS (France)

Nowadays, one out of six people are affected by mental health problem in EU every year, which costs EU more than 600 billions of euros. It is within this mind that this symposium was organized to discuss susceptibility, protection, and resilience factors for mental health. These factors can be brain-related (genetics, stress, nutrition, perinatal infections or environmental hazards exposure), mind-related (emotions, behavior, interactions with others) or societal (cultural, economic, political, environmental). Our aim during this symposium can be divided in five objectives:

- (i) To review the mechanistic understandings of mental disorders
- (ii) To review the role of vulnerability and protection factors in mental disorders
- (iii) To review the importance of resilience in mental health
- (iv) To develop prevention, intervention and care strategies for mental disorders
- (v) To discuss the opportunity of a call for research on vulnerability, protection and resilience in mental disorders

Foresight symposium 2022

Common factors in vulnerability and resilience in mental health: General psychiatry & focus on addiction and eating disorders

Pr. Chantal Martin-Soelch (Switzerland)

1) Resilience

The easiest way to introduce the concept of resilience is to contextualize it in trauma. There are several kind of traumas, which are more or less likely to lead to post-traumatic stress disorder (PTSD). For example, living a natural disaster has a lower probability to trigger PTSD than suffering a rape. In the context of trauma, resilience corresponds to the ability not to develop a PTSD or suffer mental health problems, but to follow a stable trajectory of healthy functioning after a highly adverse event: to react to the trauma with an acute response stress, that will quickly diminish. Resilience allows a dynamic system to adapt successfully to disturbances threatening its viability, function and development, and to harness resources in order to sustain well-being. In other words, resilient individuals will not develop functional impairment or psychopathology following highly adverse events.

Resilience is regarded as either a process or a trait, that is more or less thick across individuals and that varies throughout life phases or between domains (work, family, etc.) in an individual's life. Resilience has also been conceptualized as a mediating/moderating factor after the exposure to stress, protecting from the potential development of psychopathological consequences. Several factors can influence resilience, and among them the most important ones are social support, cognitive flexibility, and a properly functioning reward circuit.

2) Reward circuit and mental disorders

Since its discovery in the years 1950's, the brain reward circuit has been extensively studied and the different structures composing it have been well described. Its organization is similar between humans and animals, and in both it reacts when the individual is exposed to a reward (positive reinforcer and incentive stimuli) to enhance positive mood or motivation. Briefly, the mesolimbic dopaminergic system, and particularly the nucleus accumbens within the striatum, is crucial for reward processing. The orbitofrontal cortex is involved in processing the value of the reward. Reward circuit is therefore essential for surviving, as it provides individuals the motivation to search for food, reproduce, or avoid threatening situations for instance. Overall, there is a clear link between the brain circuit, the neurotransmitter dopamine and the behaviour.

Impaired response to reward are evidenced in several mental disorders such as substance use disorder, depressive disorder, eating disorders, PTSD, and psychosomatic conditions like fibromyalgia. It constitutes an interesting crosspoint between different psychopathologies, and thus processing of responses to reward is one of the research domain criteria in psychiatry with a transdiagnostic perspective.

a- Reward system and substance use disorder

Physiologically, a reward enhances the rise of dopaminergic neurotransmission in the nucleus accumbens, thereby promoting positive reinforcement, motivation and a positive mood. However, an addictive substance is able to hijack the reward circuit and deteriorate the response to reward. For

instance, a cigarette smoker will be less sensitive to a monetary reward, with less dopaminergic neurotransmission and a lower mood increase. This reduced response to reward and diminished dopamine function is evidenced for several types of substance use disorder, even in the case of behavioural addiction. Neurobehavioral models of substance use disorder conceptualize the « anti-reward » system as a mechanism in the development of this pathology. Addiction is a pathology that exhibits a strong family risk, notably for alcohol, with a critical age range for its development (adolescence). However, there is no demonstration at this day of a genetic inheritance for resilience.

b- Reward system and depression

In case of major depressive disorders, one of the main characterizing symptoms is anhedonia. It is the inability to feel pleasure in normally pleasurable activities. As depression involves a lowering of dopaminergic neurotransmission, the appearance of anhedonia can be linked to the reward system. Moreover, patients suffering from depression show less activity in fMRI in the nucleus accumbens. These two mechanisms could underlie the presence of anhedonia in depression.

c- Reward system and eating disorders

Because of crosstalk between the homeostasis system and the reward system, this last one influences food intakes. First because it provides the motivation to search for food for example as explained above, and second because some molecules can interact with both systems. For example, anandamide is implied in the regulation of food behaviour, and, as an endocannabinoid, it can interact with the reward system. Eating disorders can be associated with impairments in the reward system, in particular with regard to mood regulation and anhedonia. It is also interesting to notice that there is a certain form of vulnerability to eating disorders, as the main predictor of it is having a sibling with it.

3) Resilience and vulnerability

Impaired reward responses are strikingly evidenced in several mental disorders. However, it does not become immutable, and it is possible to fix the reward circuit. For instance, in case of major depressive disorders, psychotherapy can restore neural responses to reward. Similarly, it is possible to restore dopamine function after smoking cessation. However, evidences are in favor of the hypothesis according to which individuals are born with a vulnerability to some psychopathologies. For example, reduced responses to reward are evidenced in offsprings from parents suffering from mood disorders. Also, remitted PTSD patients show blunted responses to reward. Recovered anorexia patients show reduced activation to sweet taste and increased activation to monetary reward. Finally, an imbalance

Foresight symposium 2022

between stress reactivity and reward responses can be used as a predictor for the development of psychopathological symptoms. Considering these elements among others, researchers hypothesize that a properly working reward system acts as a resilience factor, and that interactions between stress and reward predict vulnerability to stress and adverse response to traumatic events. Moreover, offsprings of parents with depression have three times higher risk of developing depression themselves. It would be thus interesting to study these populations to answer questions about resilience and vulnerability factors, but it is highly complicated to gather wide samples in these populations.

4) Implications for future research

Reward responses can be used as an outcome measure to establish the effects of an intervention. It is also possible to conceive interventions targeting reward responses, either to prevent or treat psychopathological symptoms. For instance, behavioural activation therapy can reduce depressive symptoms and restore the striatal response to reward. A mindfulness based cognitive behavioral therapy intervention can restore striatal responses to positive emotions in a group of cigarette smokers and opiod users. In addition, preventive resource-oriented cognitive behavioural therapy-based stress management intervention was shown to increase the individual resources and to increase the perception of rewards in everyday life.

Future challenges in this field of research will concern new study designs and samples. There is a crucial need for prospective and longitudinal studies, multi-center or cohort studies taking in account cultural differences. Those shall be led using a transdiagnostic approach, to identify specific mechanisms. It will hopefully facilitate the birth of treatment targeting specific mechanisms. Doing prospective studies involves the identification and investigation of vulnerable people. Using multi-modal approaches with behavioural and clinical measures will help this purpose. It will allow the development of stress prevention programs to limit the emergence of mental disorders. Such programs have been used in a population composed with students (« GE-DE-stress program »). It improved many aspects of their life, including the quality of life general, self-compassion, sense of coherence, perception of criticisms and emotions regulation in everyday life. It is also important to identify and investigate samples at higher risk to be exposed to stress. These can be studied by combining lab measures with ambulatory assessment or Ecological Momentary Assessment (EMA), where individuals fills self-report measures in their everyday life several times a day. It could help developing large-scale interventions and culturally sensitive interventions. Finally, the investigation of trauma survivors is critical, by setting up interdisciplinary approaches, such as the coordination of preclinical and clinical research, or the use of gut-brain and neuroendocrine measures. This will help the understanding of mechanisms underlying resilience, and therefore will greatly improve the prevention of mental disorders.

How is the interaction between the environment and mental illness mediated in the brain?

Pr. Andreas Meyer-Lindenberg (Germany)

1) Urbanicity: a risk factor for mental health disorders

As demonstrated within the cities of Chicago and Mannheim, urbanicity increases the risk of mental illness. Moreover, living in a big city lowers happiness, even though urban populations are on average more educated and richer than countryside populations. Furthermore, whereas life expectancy tends to increase with time, this is not the case in some cities such as Mannheim where it has been stagnating for years. Considering the ongoing increasing of urban population, it is crucial to understand how urbanicity constitutes a risk factor for mental health.

In a functional MRI experiment, researchers were able to show that brain regions linked to social stress are hyperactive in city dwellers. It was also shown that the number of years spent in a big city tunes cingular activation during social stress processing. In addition, urban birth has an impact on brain structure: it diminishes the gray matter volume in the perigenual anterior cingulate cortex. For first and second-generation migrants, the risk of developing schizophrenia is 2.7 times higher than for the rest of the population. This is partly linked to the fact that migrants must live in a society with social codes differing from where they grew up. By performing fMRI during a social stress, researchers showed that second-generation migrants exhibit altered social stress processing, with dopamine hyper-release and cingular hyper-activation. All these elements provide evidence that urbanization constitutes an environmental risk factor for mental illness.

2) Brain mechanisms

Established genetic risk variants in OXTR and CACN1AC are linked with social dysfunction and affect the functional coupling between the anterior cingular cortex, hypothalamus and amygdala. Furthermore, urban upbringing and social status processing, both considered as environmental risk factors, activate the anterior cingular cortex. There are also significant differences in amygdala habituation to threatening stimuli between a healthy person whose amygdala activity rapidly decreases, and a patient suffering from bipolar disorder for whom it is not the case. Moreover, amygdala habituation is negatively correlated with Childhood Trauma Questionnaire score. All these elements indicate that environmental risk factors for mental health disorders affect neural circuits involved in the regulation of negative emotion and stress.

Overall, research indicates risk and resilience are linked to perigenual anterior cingular cortex and regions regulated by it such as ventral striatum and amygdala. A resilient brain would exhibit a bigger hippocampus, ventromedial prefrontal cortex and perigenual anterior cingular cortex. These elements would provide a dynamic stress response with a greater safety-related activity, thereby enhancing regulation of the amygdala. Amygdala would thus exhibit a discriminative and lower affective activity, allowing to react properly to a stressor.

Foresight symposium 2022

3) Primary prevention

Identification of individual vulnerability and resilience factors is crucial considering the increasing and fast-paced urbanization. Designing new multimodal cohort studies will be important to characterize environmental exposure and the way it affects individuals. One example of these studies is the PEZ-study, which aims at mapping how subjects feel at different places and times of the day on a phone application. Subjects then participated in fMRI analyses. This study demonstrated that social interaction enhances well-being and is associated with increased anterior cingulate gray matter volume. It also showed that non-exercise activity such as walking improves well-being as well. Subjects with smaller ACC who do not move much would feel even less energetic than subjects with a normal ACC who do not move either. However, if they move more, they would feel much more energetic than someone with a normal ACC who moves as much.

Nature exposition leads to a lower perfusion of the perigenual anterior cingulate cortex, less rumination, more wellbeing, as well as a better episodic memory. People on whom nature has the greatest effect are those with an altered prefrontal cortex activation and those who are encountered in the city-center. Of interesting note, as the impact of nature is mostly visual, virtual reality can be used to compensate the absence of nature.

Research efforts helped identifying resilience factors such as nature, social interaction and non-exercise activity. As of now, primary prevention and interventions need to be designed around them, to compensate risk factors of mental illness, which are favored by climate changes.

Early interaction and bonding

Pr. Ruth Feldman (Israel)

1) Behavioral synchrony during life

Bonding with other individuals is a defining feature of mammals. Indeed, mammals are born with an immature brain and therefore maintain contact at young age with their nursing mother. This relationship allows the development of biobehavioral synchrony. Biobehavioral synchrony is the coordination of biology and behavior between mother and infant during social contact. A coordinated moment leads to the synchronization of heart rate (autonomic synchrony), to brain-to-brain synchrony, and to the coordinated release of oxytocin (hormonal synchrony) in the brain of both mother and child.

Synchrony is first developed during the sensitive period, from birth to nine months old when the prefrontal cortex (PFC) shows a first reorganization. At birth, behavioral synchrony evolves through species-specific parental behavior, and then through non-verbal coordination and later nonverbal-mutuality when the child begins to participate in social moments with his mother at three months. Overall, this period provides the foundation for the child to bond with other persons, as synchrony happens throughout all life, not only with parents but in any significant relationship (friendship, love, or even between a therapist and his patient for example). When the child grows up, synchrony is favored by symbolic expansion and empathic dialogue. When reaching the adult-age, synchrony happens in adult-adult relationship through reciprocity, sharing multiple perspectives, or intimacy. It is important to note that behavioral synchrony is not immutable, and thus can be ruptured and repaired. If synchrony is not strong enough, depression may occur. On the opposite, hyper-synchrony enhances anxiety. Therefore, the mother-child bond is strongly linked to resilience, and behavioral synchrony development constitutes a factor of resilience. Of important note, this is the case for mother-child bond, but also for father-child bond, even for adoptive parents.

2) Biological basis underlying synchrony and bonding

a- Oxytocinergic system

The oxytocinergic system is very ancient in evolution, and originally had a role to play in stress management. In mammals, it gained a role in bond formation. Indeed, in mammals, oxytocin is released during touch, contact or synchronous interactions with other. It is particularly high during the first three months of a relationship. Oxytocinergic system becomes disrupted when bonding fails, for example because of a post-partum depression, a premature birth leading to child/mother temporary separation, or an environmental stress.

It is organized in the brain in the following manner. The oxytocin-prime hypothalamus sends projections to the amygdala (involved in fear) and the subcortical dopamine network (involved in bliss), to form the subcortical network underpinning maternal care. Oxytocin receptor in nucleus accumbens

Foresight symposium 2022

(NAcc) neurons also co-express for dopamine and this support bond formation. When dysfunctional, it leads to mental disorders such as depression or addiction.

The behavior of a parent of a child with autistic spectrum disorder is similar to the one of a parent with a neurotypical child. However, the children is less responsive so there is less synchrony. For an interaction with his parents, an autistic syndrom disorder child will start with a low level of oxytocin, which will become optimal after 20 minutes of interaction. However, it will be impossible to sustain this level, which will then rapidly decrease. This dysfunction in oxytocin underlies the difficulty there is for a child with an autistic spectrum disorder to bond with others.

b- Brain basis of mammalian parenting

Mammalian parenting implies amygdala, hypothalamus and limbic reward circuit. In humans, there is a cortical implication. The human brain system for parenting is divided in three parts:

- The empathy network: involved in the ability to feel infant pain, emotion, and ground experience in present moment. Brain structures involved are anterior cingular cortex and anterior insula.
- The mentalizing network: involved in the understanding of infant intention and communication. Brain structures involved are superior temporal sulcus, superior temporal gyrus, precuenous, temporo-parietal junction and ventromedial prefrontal cortex.
- The emotion regulation network: plays a role in multi-tasking and long-term goals with the implication of frontopolar cortex and medial orbitofrontal cortex.

c- Human attachment network only activates fully during synchronous social moments

Social moments induce neural synchrony, particularly in amygdala, insula, and temporo-parietal junction, which register temporal regularities. A « synchronous mother », who listens and adapts to the infant cues, will exhibit a good nucleus accumbens activation as well as the activation of the three parental brains. However, a dysfunction of this wiring will lead to a disturbed mother behavior. For example, an « intrusive mother », who stimulates the infant even during resting time, will exhibit an activation of the amygdala, which will not be downregulated as it should be. An « unavailable mother », for example on her phone, will not exhibit activation of the parental brain in reaction to an infant cue, as it is the case for an « unresponsive mother », suffering from post-partum depression for example.

There is a cross-generational transmission of neural attachment network. Children create a representation of their mothers, which will not change throughout life, and will guide their way of engaging new relationships. Brain-to-brain synchrony triggers social contact in mammals, as demonstrated in mice with the following experiment. If electrodes are inserted in two mice's brain, the synchronous stimulation of these respective mice's brains will lead to interaction, whereas stopping the stimulation will lead to the stop of the interaction. Children activate same attachment

network to own mother-child interaction across ages as the parent. Activations to attachment stimuli across the 20-year span is time-invariant despite large variability in nature of stimuli.

d- Olfactory communication in infant

Newborns detect maternal amino smell, which has several effects on them. Indeed, maternal odors reduce attention to face, reduce fear, and increase positive arousal and social behavior. It was thus hypothesized that maternal body odor would facilitate infant-adult neural synchrony. Researchers designed an experiment to study this phenomenon. Mother participating to this study had to sleep in the same t-shirt for two nights. Then, this t-shirt was conserved in a closed jar. Later, the baby is in presence of his mother, who is face to him or turning her back. Otherwise, the baby is with a stranger, who had a baby in the same period of time, in the same conditions, with or without the t-shirt on the baby chair. During these sessions, neural data was recorded from both the baby and the mother or stranger. Conclusions of this study were multiple: i) face-to-face position increases neural synchrony, ii) neural coupling is stronger with the mother compared to the stranger, iii) maternal body odor levels out differences between mother and stranger. This study also helped the detection of a two-brain neural mechanism by which mothers tune the infant's brain to social life: right-to-right brain theta synchrony between the adult's central region and the infant's occipito-temporal region.

3) Future implications for resilience research

The bonding developed between a parent and infant conditions the future ability of the infant to, later, bond with other persons. This ability plays a role in resilience to mental health disorders, making behavioral synchrony a resilience factor. Research on this topic led to the development of synchrony-based psycho-educational interventions to help mothers suffering from post-partum depression to bond with their babies. However, it is still needed to design studies with young subjects to explore behavioral synchrony, oxytocin, and the affiliative brain. These three elements are the basis of affiliative bonds. Biobehavioral synchrony helps the coordination of biology and behavior during social contact. It develops the mother-infant bond, and can happen during non-verbal communication or mature dialogue. The affiliative brain and oxytocin are involved in sociality, stress management, and well-being that sustains attachment. Affiliative brain, based on mammalian maternal brain, allows romantic love and friendship. Finally, oxytocin sustains spirituality, sense of belonging, empathy and transcendence. In the context of group living, these three elements participate to the moral elevation of cultural rituals, the social cognition and theory of mind, the in-group cohesion and out-group derogation, and to brain-to-brain synchrony. These being essential elements of one's life and promoting mental health, it is important to understand mechanisms that underlie them.

Foresight symposium 2022

Role of metacognition in protection, resilience and vulnerability to mental disorders

Pr. Francesca Maria Bosco (Italy)

Metacognition is an innate human ability necessary for interacting with other persons in a social context. It is notably composed of theory of mind (ToM) which enables self-knowledge and the understanding of other persons' beliefs, emotions and desires. ToM constitutes a protective function against psychopathologies, and therefore it is important to ensure its good development during adolescence, a critical period for psychopathological development.

ToM impairments have been described in many psychiatric disorders such as schizophrenia, alcohol abuse disorder, eating disorders, etc. Hence, ToM constitutes an interesting object of study in the scope of psychiatric disorders development. However, only few tools have been developed to assess metacognition in patients. Moreover, the existing ones are rarely translated in other languages, making it complicated in this field of research to study cross-cultural aspects. There is also a crucial need for a greater number of reviews and meta-analyses about the more basic components of metacognition. These research advances will allow the development of programs aiming at improving metacognitive skills or preventing a metacognitive decline, and tests to evaluate the recovery processes of metacognitive deficits.

Post-traumatic stress disorder and resilience

Pierre Gagnepain (France)

1) From trauma to PTSD

Trauma is the sudden or repetitive exposure to sexual violence, serious injury or actual or threatened death. It can be through either a direct personal exposure, a witnessing of trauma, or experiencing through close individual or an extreme exposure to aversive details of a traumatic event. When the trauma is too strong to be handled, the victim develops a post-traumatic stress-disorder (PTSD). The appearance of PTSD is characterized by several symptoms. First, there is a persistency of intrusive traumatic memories. Those are brief sensory fragments of the traumatic experience triggered by reminders weakly connected to the trauma, with a lack of time-perspective, a decreased awareness of present surroundings, and a sense of current threat. Patients suffering from PTSD will also develop hypervigilance with increased levels of arousal and reactivity (hyper-arousal). Taken together, these symptoms will lead persons with PTSD to avoid anything that could remind them of the trauma, be it places or activities for instance. Others symptoms of PTSD are sleep disturbances, poor concentration, dissociation, and a dysregulation of emotional states such as fear, anger, guilt, and shame.

PTSD can be seen as an emotional disorder characterized by a dysregulation of circuits that anticipate, react, evaluate and regulate threat. For instance, a hyper-responsivity to threat in sensory and emotional circuits together with a lack of top-down modulation of the resulting fear or emotional response is often observed in individuals with PTSD. Other models view PTSD as a memory disorder and focus on the persistency of intrusive memories due to an initial overconsolidation of sensory and emotional elements in the memory traces. This is followed by a failure of the extinction or updating of the original traumatic memory traces while in a safe environment, together with an abnormal and exaggerated processing of contextual reminder of the trauma. Such deficits are primarily rooted in the dysfunction of the hippocampus and its interaction with the ventromedial prefrontal cortex (vmPFC). To illustrate these two models, avoidance can either be viewed as a maladaptive coping mechanism resulting from abnormal threat computation and evaluation, or as a memory deficit illustrating the failure of the hippocampus to discriminate and separate safe environmental cues from threatening traumatic cues and resulting in an overgeneralization of fear.

Now the challenge is to understand why some individuals will develop PTSD after trauma while others will remain unaffected; in other words, why some individuals are resilient whereas others are vulnerable. It would be of great interest to understand the pathological processes, but also the protective factors allowing some individuals to remain healthy after a trauma.

2) Factors of resilience and vulnerability after trauma

Active processes of adapting to stressors to maintain homeostasis, termed allostasis, characterize a form of physiological resilience. Pathological processes involve a dysregulation of this protective response to stressors across various interacting levels, including the neuroendocrine system, the autonomic nervous system, the metabolic system and the immune system. Studies have been

Foresight symposium 2022

conducted to understand the factors that make individuals vulnerable to trauma and stress-induced alterations in the brain. These factors are various: some are genetic, social, or environmental, depend on life history, on psychological traits, or on peripheral and central markers of the nervous system.

However, resilience cannot only be defined as being the flip-side of vulnerability. Resilience describes the ability to bounce back and maintain good mental health after a trauma. It is a dynamical feature that is individual-dependent and evolves throughout life. In this context, resilience should not be qualified as a static property of the individual, but rather as an outcome depending on dynamic process of adaptation to stress. This dynamic process may have a trajectory of undisturbed, stable mental health during and after a potentially traumatizing event or a prolonged period of adversity, or may also consist of temporary disturbances followed by a relatively rapid, successful recovery. Overall, resilience is a mutable and self-organized mechanism acting upon the negative effect of stress, whose maintenance or acquisition precedes recovery from an exposure to trauma.

Resilience researchers are not interested in pathophysiology; instead of investigating the mechanisms that lead to stress-related illness, they investigate the mechanisms that prevent illness. This development constitutes a paradigm shift from disease- to health-oriented research in the fields of clinical psychology and psychiatry. This shift is, however, not yet complete. The brain constitutes the primary interface between a given stressor in its physical and social context, and an individual's physiological and behavioral accommodation to that stressor. Therefore, the brain and the neurocognitive response to stress is probably one of the primary mediator of allostasis and resilience. Yet, little is known about brains mechanisms enhancing resilience after trauma. It is therefore crucial to articulate resilience research around neural mechanisms limiting the negative impact of stress-related dysfunction.

Toxic stress heightens sensory cortical excitability, thereby inundating higher-order processing and potentially causing global hyperactivity, disinhibition and widespread dysfunction. Through the glutamate system, acute and chronic stress alters synaptic function (synaptic transmission/plasticity), neuroarchitecture (dendritic morphology, synaptic spines) and neurogenesis. These stress-induced alterations are of particular importance in the hippocampus, a subcortical structure important for memory function. Hyper-excitability in threat and memory circuits leads to an over-consolidation of sensory and emotional elements, an alteration of contextual processing, a shift from a hippocampus-based memory trace to an amygdala-striatal representation reducing opportunity to update the traumatic engram through reconsolidation. All these disturbances, initiated by stress-induced hyper-excitability, contribute to the development of intrusive and traumatic memory. Hence, mechanisms that support the gating of hyperexcitability and the flexible deactivation of fear and memory processes are to be investigated as general mechanisms of resilience.

These forms of regulatory control of excessive and interfering activity is permitted by the frontoparietal control system and inhibitory control. The frontoparietal control system supports the flexible regulation of mental processes and behaviors according to cognitive, emotional or behavioral goal. A fundamental mechanism implemented by this network is inhibitory control. It enables humans to stop strong interfering activity or initiated response when they become inappropriate.

The process of stopping memory retrieval plays a central role in memory suppression. Memory suppression is a process that can be viewed as a potential resilience mechanism. The research project REMEMBER (Resilience and Modification of brain control network novEMBER 13) studies the victims

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of the terrorist attack that took place in Paris on November 13th 2015. It is a multiwave longitudinal neuroimaging study, with a group of direct survivors from the terrorist attack, and a group of non-exposed control participants. Both structural and functional brain imaging data have been collected at about 1 and 3 years following the attacks. This study focuses on the role of memory control mechanisms related to active forgetting, in the variations of response to trauma, and shows that the presence of inhibitory coupling between the prefrontal cortex and the hippocampus during the control of unwanted memories is fundamental to understand resilience after trauma. Furthermore, the magnitude of inhibitory control was correlated with a greater volume of the hippocampal CA1 region in individual without PTSD. Although this needs to be confirmed in further studies, it might suggest that memory control process reflects a resilience mechanism that insulate the hippocampus against stress-related alterations and might limit the formation of the traumatic engram.

3) Upcoming challenges for Human research on resilience after trauma

First of all, there is a need for a better characterization of the relationships between the ecological system of resilience with the neural mechanisms associated with resilience that break the negative effect of stress on the human brain. The ecological system of resilience should be explored through several dimensions: individual, social, environmental and societal. All of these dimensions must certainly interact in a very complex way, which illustrates the multidimensionality of resilience. This complexity is especially pronounced when we consider traumatic events that have a collective resonance in the society as we sadly have to face more and more. The way we conceptualize and recall these events in the social spaces has a profound influence on individual memories and future research would also need to apprehend the societal and collective dimension of resilience. The integration of a traumatic event to collective narrative may promote forgetting at the individual levels, by harmonizing individual memories and promote forgetting of individual idiosyncrasy. It may also confer a social value of the individual experience, thereby facilitating positive appraisal and traumatic memory integration to a healthy declarative memory system.

Another challenge is to design longitudinal studies, with as many data-points as possible to ascertain the temporal dynamics of resilience mechanisms. These could lead to a better definition of the many phases of resilience. For instance, resilience may involve a resistance phase characterized by the lack of key molecular and physiological abnormalities, that impair their coping ability. Disturbances or collapses may explain the development of the pathological outcomes, and recovery or even reinforcement (the presence of distinct adaptive mechanisms engaged to counteract maladaptive changes) may then explain the return to a positive outcome. Such longitudinal designs, however, may be problematic to adopt depending on the clinical population considered, and the research environment.

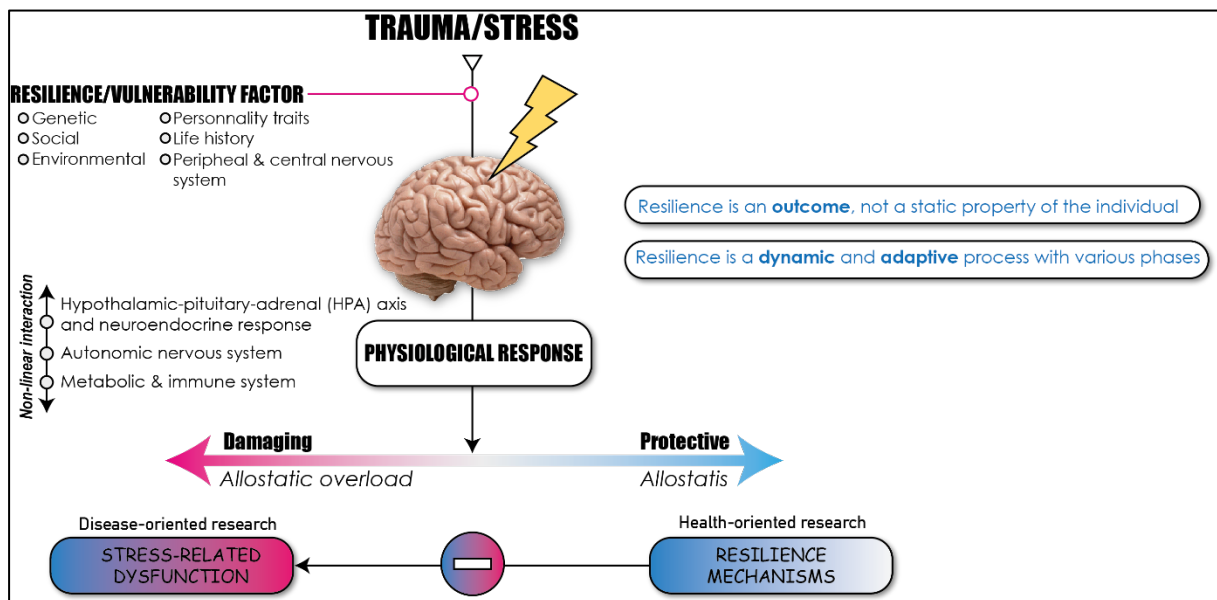
Measurements must also occur as close as possible to the trauma, which constitute a big challenge. Moreover, designing prospective studies would bring precious information on resilience but limits the population that can be studied (militaries, police officers, etc.). Furthermore, as resilience is likely a

dynamic process reflecting multiple mechanisms operating on different timescales, modeling the temporal trajectory may be particularly informative about the underlying mechanisms. This endeavor

Foresight symposium 2022

will require dense sampling of intraindividual data across time and the application of emerging statistical techniques for modeling trajectories.

Another very important aspect is to rely on causal mapping. One solution is to measure in parallel of resilience mechanisms, their impact on the physiological and neural markers of stress-related dysfunction. Although, this is easy for physiological markers, this is quite a challenge for the neural marker of traumatic memory. There is a crucial need for human studies that track the neural implementation of traumatic memory in the human, but these are challenging for technical and ethical reasons. Furthermore, as measurements of resilience mechanisms on one hand, and physiological markers of stress-related dysfunction on the other occur at different time-scale, measuring their mutual influence might be challenging. One interesting solution to increase causal mapping is to develop designs with brain or cognitive stimulation of resilience mechanisms, which may help to gain new insights into the resilience functions of specific brain areas and increase translational research.



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Role of immune system in resilience and susceptibility in mental disorders

Pr. Marion Leboyer (France)

1) Interaction between nervous and immune systems

Infections, pollution, urbanicity or stress and trauma constitute factors to which everyone can be exposed throughout life, which affect the immuno-genetic background. This impact can notably lead to low-grade inflammation, which has an effect on: (i) blood through immune cells and oxidative stress, (ii) brain by affecting connectivity and activating microglia, (iii) metabolism through kynurenine or leptin, and (iv) gut-brain axis by causing dysbiosis or leaky gut syndrome. Because of its ability to sense microbes or stress and report it to the brain, the immune system is now regarded as the seventh sense of the brain. Immunomodulatory proteins have regulatory functions in the brain. For example, microglia factors model circuit connectivity, cytokines regulate neuronal differentiation, complement proteins kill damaged neurons, and the major histocompatibility complex (MHC) proteins modulate synaptic plasticity. Moreover, neuronal factors play major roles in the immune system, such as leukocytes that possess receptors for classical neurotransmitters, and blood-brain barrier, which regulates endothelial passage of immune cells.

Mental disorders are linked with an abnormal level of inflammatory cytokines, reflected by the level of C-reactive protein (CRP). It is especially high in schizophrenic patients who are resistant to psychotropic treatments. An elevation of CRP level is also associated with a reduced functional connectivity within abnormal regional circuits associated with depression. Still in the context of depression, inflammation causes neurotransmitter abnormalities. Cytokines within the brain lowers monoaminergic neurotransmission, which is the main target of psychiatric treatment. Monoaminergic depletion causes anxiety, anhedonia, anergia, lethargy and depression. This depletion, together with microglial cell activation, lead to NMDA hyper-reactivity associated with impulsivity and suicidality. Overall, there are clear evidences for interactions between the immune and nervous systems and for their involvement in psychiatric disorders. This highlights the potential role of the immune system as a factor of resilience and susceptibility to mental disorders.

a- Infections

Research shows many evidences for a link between the appearance of mental disorders and the immune system. For example, maternal infection rises the risk to develop schizophrenia (SZ) and bipolar disorder (BD). A history of hospitalization for infection increases the risk of later mood disorder by 62%. A prior hospitalization for autoimmune disorders increases the risk of later mood disorder by 45%. Infection and autoimmune disorders increase such risk in a dose-dependent manner. An example for infection enhancing the later emergence of psychiatric disorders is the *Toxoplasma gondii* infection. This parasite has a seroprevalence almost two times higher in BD patients (76.9%) than in healthy people (40%). *Toxoplasma gondii* seroprevalence has also been linked with other psychiatric disorders, like addiction or obsessive-compulsive disorder.

Foresight symposium 2022

These phenomena might be due to sequence depending on immunogenetic background when the infection or auto-immune disorders constitutes a first hit that leads to a non-resolved chronic inflammation, and then later an infection or a stress constituting a second hit leads to the emergence of psychiatric disorders.

b- Childhood trauma

Inflammation mediates early and severe stress in psychiatric disorders. A severe childhood stress is linked with many pathologies, and notably the appearance of psychiatric disorders. Following a severe trauma during childhood, there is a rise of CRP-level as well as interleukine-6 (IL-6) and tumour necrosis factor- α (TNF- α), both proinflammatory cytokines. Indeed, high levels of CRP are measured in depressed patients with a history of childhood maltreatment, as compared to those without childhood trauma exposure. It is thus possible that these elements constitute local and systemic mediators of environmental stressors. Childhood abuse diminishes the onset age of BD, and this diminution is proportional with the number of abuse subtypes (physical abuse, emotional abuse, neglect or sexual abuse) the child had been exposed to.

c- The importance of a healthy diet

Studies in murine models show that a healthy diet together with physical activity practice and enrichment in the cage resculpt neuronal morphology, and act on molecular factors rate. Indeed, it increases brain-derived neurotrophic factor and insulin-like growth factor-1 concentrations and decrease TNF- α , IL-1 β , nitrogen oxides and major histocompatibility complex class II levels for example. This enhances neuroprotection, neurogenesis, synaptic plasticity and cognitive longevity. In humans, a Mediterranean diet, considered a healthy diet, lowers both inflammation and depression. In contrast, a poor diet will lead to pathological processes affecting mental health and somatic comorbidities, and early death.

d- Fine particles pollution

Fine particles pollution exposure has dramatic consequences on individuals' health, notably through the rise of inflammation it causes. Several pathological processes reflect this inflammation. First, it causes a reduction of T-regulator lymphocytes, whose role is to maintain homeostasis and self-tolerance by suppressing the immune response. Then, inflammation also causes an increase of oxidative stress, and alters the response to vaccination. Inflammation is located within lungs, where pollution exposure causes a rise of interleukine-6 (IL-6) and nuclear factor-kappa B (NF- κ B) levels, two pro-inflammatory factors. Finally, pollution leads to systemic inflammation by causing the multiplication of T-helper 1 and T-helper 17 lymphocytes. This pollution-caused inflammation disturbs the intestinal flora, thereby causing dysbiosis or even leaky gut syndrome. It can also disturb mental health. In France, researchers showed that over the last decade psychotic relapses correlate with fine particles pollution peaks.

2) Immuno-genetic risk factors and resilience

a- The MHC-HLA complex

Susceptibility to or protection against immune-related disorders are under immunogenetic control. Indeed, immunogenetic diversity influences the type and severity of an infectious event, by modulating inflammatory response. Following an infection, pattern recognition receptors (PRRs) such as toll-like receptors (TLRs) interact with pathogen-associated molecular patterns (PAMPs). PAMPs can be bacterial lipopolysaccharides, fungi, viral envelop proteins or parasitic phospholipids for example. PRRs are widely expressed in the central nervous and gastrointestinal systems. Interactions of a PAMP with a PRR causes the rise the level of cytokines, chemokines and of their receptors, thereby causing acute or chronic inflammation. Then, there is immunomodulation with non-classical human leukocyte antigen (HLA). HLA proteins distinguish self-cells and nonself-cells, as part of the major histocompatibility complex (MHC). There, immunogenetics establish susceptible or protective patterns of neurodevelopment in early life through interactions with environmental factors. These patterns can determine future clinical profiles. Finally, adaptive immunity is set up with HLA. In case of non-resolved inflammation, causing chronic inflammation, innate and adaptive immunities are highly intertwined.

The HLA system, hosted in the MHC, is a functional bridge between innate and adaptive immunity. HAL and MHC molecules (trimeric proteins with a transmembrane heavy chain, a light chain B2M and a peptide) are present in all regions of the brain, in both glial cells and neurons, and constitute a crossroad of infection, inflammation and auto immunity. They are also key for neurodevelopmental processes (MHC expression elevated during brain development and decreased during adulthood), synapse density and plasticity and homeostasis.

This MHC-HLA region is a major region of the genome, gathering more than 250 genes with over 25.000 alleles on the shorter arm of chromosome 6. It encodes for class II HLA associated with humoral immunity and antibody production, and class I HLA associated with detection and elimination of cells and virus-infected cells tumor cells. Products of the transcription and traduction of this region's genes lead to anti-infectious responses, and can favor autoimmune disorders. Researchers performed genome wide association studies (GWAS), which are used to identify single nucleotide polymorphism (SNP) associated with a phenotype, and found strong evidence for the implication of MHC-HLA region in psychiatric disorders. Indeed, there are 6.4% associations with single nucleotide polymorphisms of the genome wide association study catalogue. However, few studies have studied the role of specific HLA alleles in psychiatric disorders, which thus remains to be elucidated.

Overall, immunity seems to act as a resilience factor through the HLA complex. Furthermore, this complex is the most associated cluster to immune related disorders such as autoimmune disorders and susceptibility to infections. However, the complexity and density of this genome region makes it complicated to study it. As the inter-ethnic diversity and because there are many genes involved, using a candidate gene approach is impossible. Moreover, GWAS is also inefficient because of the association with the chromosomic region and only 60% of the diversity is covered. Hence, there is a need to develop new methods to study HLA diversity. It is possible to use distribution analyses of haplotypes, the first step being to proceed to the analysis of the distribution of functionally relevant HLA haplotypes (ancestral haplotypes, AH). For example, 57.1 AH is proinflammatory and associated with multiple sclerosis. 8.1 AH is nicknamed the "auto immune haplotype": it is pro-inflammatory, anti-

Foresight symposium 2022

infectious and autoimmune and lacks the complement C4 gene. It is also possible to analyze functional properties, through allele expression or quantitative trait locus. Finally, it is possible to analyze circulating levels of soluble HLA isoforms.

b- Schizophrenia and the immune system

A study compared a group of schizophrenic patients and healthy controls and showed with HLA-next generation sequencing and haplotype reconstruction that schizophrenia is less associated with HLA-8.1 AH, which is thus a protective haplotype. In absence of HLA-8.1, the response to infection is inefficient with less inflammation and the presence of C4 gene complement. The role of complement C4 pathway, located within the MHC-HLA region, is multiple. At the immune, it encodes for complement proteins that destroy invading pathogens and apoptotic genes; hence, an alteration of this pathway would increase risk to infections. At the brain level, neurons and glial cells express the complement proteins. The complement system activates microglial cells and is involved in synaptic pruning during the development. Therefore, its presence leads to excessive pruning and to early age onset of schizophrenia. In presence of HLA-8.1, the anti-infection response is efficient, but there is a risk of auto-immunity and naturally lack of complement C4 cluster (localized in the HLA class III region). HLA-8.1 confers protection to schizophrenia, which means that Schizophrenic patients who do not carry HLA-8.1 possibly have a reduced response to infections (more infectious stigma), less auto-immunity, an earlier age at onset and cortical thinning. Schizophrenia are neurodevelopmental heterogeneous disorders characterized by early excessive synaptic pruning probably due to HLA/MHC genetic background followed by a succession of environmental risk factors, interacting with innate and adaptive immunity to induce chronic low grade inflammation. HLA-8.1 AH is present in 15-20% of the Caucasian population. It was positively selected during evolution given its pro-inflammatory properties, which are protective against infection. However, there are collateral complications; most often linked with autoimmune disorders such as type 1 diabetes or coeliac disease. They lack the complement C4 gene. HLA-8.1 is associated to protection to schizophrenia. The lack of C4 gene is protective during neurodevelopment, and prevents from exaggerated cortical thickness, which is associated with early onset of schizophrenia and its more severe form. It protects against infection, but provide more autoimmunity.

c- Bipolar disorder and the immune system

The allele AA for TLR4 is more prevalent among early onset BD patients. In vitro, the presence of this allele decreases TLR4 expression. It is therefore hypothesized that it may decrease the response to infectious pathogens, as it would mean less PAMP detection by TLR4. This would lead to unresolved infections events, low-grade inflammation and autoimmunity. This diminished first line response against infection is associated with immune-genetic in BD. Relapses in BD are prevented using a lithium treatment, to which some patients respond badly. The International Consortium on Lithium Genetics gathered 3193 BD patients treated by lithium for more than six months, and proceeded to GWAS to search tags for HLA implication in response to lithium treatment. They demonstrated that the gene DQB1*O2+, which belongs to 8.1 AH, provide inflammatory properties but favors a bad response to

lithium treatment. On the opposite, DRB1 AA 74 LEU/AA, which has anti-inflammatory effects and protects against autoimmune disorders, provides a good response to lithium. Hence, HLA-mediated low-inflammatory processes contribute to a good lithium response while HLA pro-inflammatory processes are associated to a bad lithium response thus overriding lithium anti-inflammatory properties.

d- Human endogenous retrovirus elements implication

Psychiatric patients show less resistance to infection with herpes, Borna disease virus 1, COVID-19, Chlamydomphila pneumonia, *Toxoplasma gondii* and HERV-W. During the COVID-19 pandemic, Taquet *et al.* did electronic health records of more than 200,000 US COVID-19 survivors. They showed that 34% suffered from a neuropsychiatric condition less than 6 months after infection, and that this was the first onset for 13% of them. It is thus interesting to determine how COVID-19 infection favor the appearance of neuropsychiatric disorder.

Infectious environmental triggers activate human endogenous retrovirus elements (HERV) in cellular genome of permissive cells. This leads to the production of pathogenic envelop (ENV) proteins, which provokes specific receptor mediated effects such as paracrine activation or inter-cell transmission. This provides a self-sustained activation feedback loop for activation of HERV elements in the genome of permissive cells. HERV-ENV toxicity is demonstrated on microglia, oligodendrocytes, neurons and peripheral blood mononuclear cells. HERV-ENV proteins are present at elevated levels in the blood of psychiatric patients. Indeed, there are elevated plasma levels of HERV-W in SZ as well as elevated levels of HERV-mRNA in SZ and BD, notably if there were pre-existing *Toxoplasma gondii* expression. HERV constitutes a link between infection and appearance of neuropsychiatric disorders. 41% of SZ patients and 28% of BD patients are HERV-positive, whereas 98% of healthy control are HERV-negative. HERV-W positive BD patients report more emotional neglect and sexual abuse as compared to HERV-W negative BD and SZ patients or healthy control, whereas emotional abuse decreases similarly between HERV-W positive BD and SZ patients. Childhood trauma may be one of events triggering reactivation of HERV-W ENV proteins expression, which in turn may maintain inflammatory responses in a chronic state. Researchers hypothesized a two-hits model where, depending on environment and immunogenetics (TLR, HLA, complement), infections like *Toxoplasma gondii* or COVID-19 together with trauma provoke the persistence of infectious stigma with low grade inflammation (elevation of CRP, IL6, IL1B, etc.), and then it primes the activation of human endogenous retrovirus. In more details, first there is a priming event during the perinatal period. There, the immunogenetic background is responsible of a decreased anti-infectious response to pathogens. Therefore, perinatal infection by viruses or pathogens is susceptible to activate HERV-W promoters, which are not methylated in embryonal cells. The priming event occurring during perinatal period can be early childhood trauma. HERV-W reactivation will then cause retro-transposition and multiple *de novo* insertions or deletions of HERV-W sequences in human DNA. Then, the triggering event can be later life infection by viruses such as COVID, and it reactivates modified HERV-W copies in brain cells. HERV-W reactivation in microglial or brain macrophage cells causes local production of envelop pro-inflammatory proteins, causing secretion of cytokines, chemokines, etc., triggering neurotoxicity.

Foresight symposium 2022

3) Future implications for research on risk and resilience factors

Identifying risk and resilience factors will improve the understanding of psychiatric disorders' causal mechanisms, thereby allowing the refinement of public health interventions toward a better lifestyle, notably in high-risk populations. The elaboration of prospective and multimodal cohort studies will help this goal. It is important to design long-term studies, to give an insight about the variation of immune dysfunction from early psychosis to onset to cognitive decline and treatment resistance. This will allow the development of interventions aiming at lowering inflammation to improve mental health. Such studies should include patients and at-risk subjects, as it will allow the investigation of determinants of wellbeing and mental health, as well as genetic factors of risk and protection. It is crucial to test the safety and efficacy of immunomodulatory treatments, and to develop services and social intervention to prevent mental health disorders. Altogether, this will reduce the burden on society linked to indirect costs, and the direct costs due to treatment costs.

It is also essential to promote basic psychological research to measure the impact of severe stress such as pandemic, war or economic recession, and to determine the factors mediating this stress. Psychological and behavioural research should be conducted regarding the treatment of consequences of stress. Another priority is to explore the consequences of an abnormal intestinal flora, in order to promote a healthy diet and to develop targeted diet and gut-brain interventions at all age. Finally, it is important to evidence the impact and cost-effectiveness of clinical interventions to improve, protect and promote wellbeing.

Finally, research articulated around the understanding of susceptibility and resilience factors to mental health disorders will allow the implementation of prevention strategies. These strategies will be at the individual level for risk factors such as obstetrical complications, cannabis use or childhood trauma, and at societal level for risk factors such as urbanicity, poverty and migration. They should allow the setting up of simple lifestyle measures allowing the diminution of inflammation, thereby promoting mental health.

Increase resilience through new technologies, new therapies and new patient care

Pr. Giuseppe Riva (Italy)

1) What is VR?

In the joint endeavor to develop new tools for mental health study and treatment, virtual reality (VR) is a perfect candidate. VR consists in using computer technology to create a simulated environment. This is achieved using special electronic equipment, such as a helmet with a screen inside (head mounted display) or gloves/joystick fitted with sensors (trackers). It differs from 3D through the sensation of presence: indeed, the patient is not a spectator but a part of the scene. As VR technology is becoming more and more democratized as years pass, prices are becoming lower and lower, making it easier to access.

2) Top-down and bottom-up processes

Changes occur through an intense focus on a particular instance or experience. Through the exploration of this experience, the patient can relive all entire significant elements associated with it, be it conceptual, emotional, motivational or behavioral, making them available for reorganization. Within this general model, there are several specific methods in clinical psychology such as the insight-based approach of psychoanalysis, the schema-reorganization of cognitive therapy, the functional analysis of behavioral therapy, the interpersonal relationship focus of interpersonal therapy, and the enhancement of experience awareness in experiential therapies. According to Safran and Greenberg, behind the specific therapeutic approach there are two different models of change: bottom-up and top-down. Bottom-up processing begins with the focus on perceptions and sensations and leads to change at the behavioral and conceptual level. Top-down change usually involves exploring and challenging tacit rules and beliefs that guide the processing of behavioral planning and leads eventually to changes in sensation processing. The second system is reasoning: it generates judgments that are always explicit and intentional, whether or not they are overtly expressed.

The dissociation between verbal knowledge and task performance show the existence of two different cognitive systems. People learn to control dynamic systems intuitively without being able to specify the nature of the relations between the system, for example with a bicycle. On the other hand, people can describe the rules by which the system operates without being able to put them into practice, for example with the driving exam. VR allows targeting these two elements simultaneously.

3) Virtual reality as a cognitive technology

Different meta-analyses, systematic and narrative reviews indicate that VR compares favorably to existing treatments in anxiety disorders, pain management and eating and weight disorders, with long-term effects that generalize to the real world. Furthermore, they suggest a clinical potential in the treatment of psychosis and in the pediatric field. In anxiety, one of the main aims of treatment consists

Foresight symposium 2022

in coping with feared situations. This is achieved through “exposure”, a treatment used precisely to activate pathological fear structures in order to disconfirm sufferers’ beliefs and teach them to cope with phobic situations. Exposure procedures involve presenting a person with anxiety-provoking material (situation, objects, etc.) for a long enough time to decrease the intensity of their emotional reaction. Usually, the patient is exposed to the feared situation in a gradual manner, for example by beginning with thinking about the feared situation, then by seeing a representation of it on a screen, and so on. However, *in vivo* exposure has a number of limitations and VR is considered a viable alternative to this technique. For example, US army exposes its soldiers to the trauma they suffered through VR to treat their PTSD. Another demonstrated use of VR as a treatment is to diminish vertigo, by simulating for example a high walkway to cross.

The long-standing classical view of cognition maintains that we experience the world in three steps: i) receive input from our environment, ii) process input in higher levels of brain, iii) respond to input accordingly. However, an alternative theory about predictive coding has been gaining ground as a more accurate explanation for what is going on: not only does information flow from our senses to our higher faculties, but those higher faculties also often predict the input from our environment, thereby influencing our perception of it, before we actually sense it. Different visions from cognitive sciences (situated cognition, embodied cognition, enactive approach) suggest that cognition is no more the simple performance of formal operations on abstract symbols, but has instead deep roots in sensorimotor processing and simulation. This would be allowed by a common coding shared by perception, action and concepts. This vision is supported by the discovery of bimodal neurons like mirror neurons and canonical neurons. Mirror neurons are a specific class of neurons that discharge both during a motor act execution and the observation of a similar action by others. Canonical neurons are a specific class of neurons that discharge during motor act execution and in response to the presentation of 3D objects supporting the same motor act.

4) Predictive coding helps telepresence

Predictive coding is an emerging trend in the neuroscience field. It hypothesizes that our brain is actively maintaining an internal model (simulation) of the body and the space around it, which provides predictions about expected sensory inputs and tries to minimize the amount of prediction errors. Predictions are based on a Bayesian model: the probability expressed a degree of belief in an event. The degree of belief may be based on prior knowledge about the event (memory), or on personal beliefs (cognition and knowledge) about the event. During the setting up of an action, a sensory prediction of the outcome of the action (simulation) is produced along with the actual motor command. The result of the comparison between the sensory prediction and the sensory consequences of the act can then be used to track any possible variation in its course. If the sensory consequences are the predicted ones, there is the feeling of presence. If they are different, there is a break in presence. There, attention and reasoning are required to identify the discrepancy. Of important note, impairments of predictive coding are believed to be behind several pathologies, such as autism, schizophrenia or eating disorders.

VR experience tries to predict the sensory consequences of movements showing to someone the same scene he or she will see in the real world. Like the brain, it maintains a model (simulation) of the body

and the space around it. This prediction is used to provide, using VR hardware, the expected sensory input. The more the VR model is similar to the brain model, the more the individual feels present in the VR environment. To sum up, telepresence is the ability of a technology to simulate the predictive mechanisms of the brain. If the prediction is perfect, there is the feeling of presence and disappearance of mediation. Some studies have confirmed that VR systems can be effective in the rehabilitation of different neurological diseases and can be useful for both children and adults. Thanks to the similarities with the functioning of the brain, VR implements specific cognitive and behavioral functions, such as executive functions, attention, spatial cognition, perceptive abilities, memory, language and psychosomatic anxiety. Thus, scientists can use it to monitor, manipulate and increase the patients' interaction with their environment, promoting functional recovery. Furthermore, thanks to the several likable activities, VR allows increasing patients' motivation and active participation.

5) Virtual reality application examples

a- Anesthesia

Immersive VR can be used as an anesthetic, as it modifies the neural areas of pain (measured using a PET). This effect is not observed with videogames. This might be due to the fact that VR hacks predictive coding system, suggesting that the patient does no longer feel present in his real body, and therefore does not feel pain. This phenomenon can be viewed as the opposite of phantom limb, where a subject experiences pains in the missing limb after amputations.

b- Obesity and eating disorders treatment

VR allows the patient to experience a different body, an experience called "body swapping". This is done by using a visual and tactile synchronization. A case study with a super- obesity case (body mass index = 60) and a study with anorectic patients provide a preliminary support to this technic. In just one session of body swapping, it is possible to reduce significantly body distortions as demonstrated in a preliminary study. A case study including one-year follow-up of an anorectic subject with three sessions of body swapping included in a classical cognitive behavioral therapy program showed this protocol could significantly reduce body distortion. At the beginning, the patient overestimated the dimension of her hips as 94.44% bigger than reality, and at follow-up she estimated it close to what it actually was. However, it is important to note than VR is less effective to treat severe forms of anorexia.

c- What is next for virtual reality?

Up to now VR has been used to simulate external reality, to make people feel real an environment that is not really there. Now, a new approach named "sonoception" has been developed. This uses sounds and vibrations for simulating and stimulating one's internal reality (proprioception, interoception and vestibular input). This aims to make people feel "real" what they are not feeling, by hacking directly predictive coding mechanisms of their inner body (stomach, heart, and ear).

Foresight symposium 2022

Panel discussion with representatives of European patient organizations

Peter Kinderman, Mental Health Europe (MHE), Raluca Nica, Gamian Europe

The Foresight symposium was concluded by a panel discussion with representatives of MHE and Gamian Europe, providing a patient view on the research on “Mechanisms of Resilience and Susceptibility in Mental Health” and pointing the necessary efforts to improve patients’ life.

Raluca Nica very well explained the importance of studying resilience in mental health, as summed up below:

Resilience is a human capacity to adapt swiftly and successfully to stressful events and manage to revert a positive state. It seems to be involved in psychopathological process for mental disorders. High level of resilience works as a protective factor and lower level of resilience increases vulnerability for developing pathological consequences of adverse events. In resilience research, there is a need to focus on evidencing that resilience is modifiable, to open up possibility for novel therapeutic interventions. The pathways to resilience for positive outcome are multidimensional, and there is therefore a need to study multiple variables of the mental illness and patient’s characteristics. This is quite important, as people with an experience of trauma significantly differs from those without, in terms of structural and functional changes in the brain. Investigating mechanisms by which trauma is associated with increased risk of mental illness would provide insight into the processes involved in the emergence of mental disorders, as well as help with the identification and development of treatment for predisposed individuals. Resilience can be embeded into the core of many treatments to achieve better outcomes. Resilience programs have potentially great benefit not only for people suffering from mental disorders but also for the general public by enhancing their ability to cope with unforeseen challenges.

Another problematic Peter Kinderman pointed out is the use of the terms “disorders”, “illnesses” or “conditions” that represent some form of pathology needed to be treated. He defended that the use of these terms keeps medicine away from the more human application of neuroscience: the idea that every human brain respond differently to challenging environment. Pathologisation may contract neuroscience and have negatve implications for care. A framework emphasizing the social determinants of mental health and wellbeing, and containing up-stream practical suggestions for primary and secondary prevention is crucially needed.

Annex

List of Participants

Speakers

Andreas Meyer-Lindenberg	Zentralinstitut für Seelische Gesundheit (Central Institute of Mental Health)
Francesca Marina Bosco	University of Turin
Giuseppe Riva	Catholic University of Sacred Heart
Marion Leboyer	Université Paris Est Créteil, AP-HP, Inserm, Fondation FondaMental
Peter Kinderman	Representative of Mental Health Europe
Raluca Nica	Gamian-Europe
Pierre Gagnepain	INSERM-EPHE-UNICAEN U1077
Chantal Martin Sölch	University Fribourg
Ruth Feldman	Reichman University

Invited guests

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Annabell Coors	University of Bonn
Hsin-Hsi Tsai	National Taiwan University
Jaanus Harro	University of Tartu
Jorge Santos Tejedor	University of Bonn
Julia Laske	University of Bonn
Julia Matthias	University of Bonn
Juliana Tavares	University of Bonn
Jung-Chi Chang	Department of Psychiatry, National Taiwan University Hospital
Karola Hüntten	University of Bonn
Liga Zvejniece	Latvian IOS
Rika Etteldorf	University of Bonn
Sermin Genc	Izmir Biomedicine and Genome Center
Inès Tran	University of Bonn
Valentina Talevi	German Center for Neurodegenerative Diseases
Muge Yemisci Ozkan	Hacettepe University
Natasa Hlavacova	Slovak Academy of Sciences, Biomedical Research Center
Igor Riečanský	Slovak Academy of Sciences, Centre of Experimental Medicine

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Leszek Kaczmarek	Nencki Institute
Brigitte Malgrange	University of LIEGE - GIGA stem cells
Joab Chapman	Sheba Medical Center. Tel Aviv University
Fabrizio Tagliavini	Department of Neurodegenerative Diseases and Director of the Division of Neurology 5 & Neuropathology at the Neurological Institute "Carlo Besta", Milan, Italy

NSC meeting NEURON

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Argo Soon	Estonian Research Council
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Francis Parlange	Swiss National Science Foundation (SNF)
Maxime Beaudoi	Fonds de recherche du Québec - Santé (FRQS)
Simona Bifulchi	Ministry of Health
Sophia Schach	DLR-PT Germany
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