The Future of Manualized Versus Personalized Psychiatry

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Rethinking Psychiatry

- Since 1952, psychiatry has undergone many changes and is emerging as a unique field in the medical area in which a novel approach is being demanded for properly treating patients.

- Not the classical "one-size-fits-all" approach, but a more targeted and tailored diagnosis and therapeutics, taking into account the complex interactions among genes and their products, environment, culture and the psychological apparatus of the subject.

Complexity of Psychiatric Disorders

- Traditionally, psychiatric diseases have been considered as a cluster of symptoms (syndromes) and psychopathology has been the gold standard to make a diagnosis.

- Psychiatric diseases are complex, multifaceted and have multifactorial pathologies, characterized by high heterogeneity and variance and, therefore, classical methods have proven to be too simple or not completely adequate to capture this complexity.

- The categorical approach, in fact, suffers from some drawbacks like circular reasoning and ambiguity.

Bragazzzi NL, 2013   Patil T et al, 2010

Bio-psycho-social Model

- The model introduces distinctions within and between biological, psychological and social components, and advocates a more holistic orientation to disease, illness and medical care.
- Post-Engelian interpretations of the biopsychosocial approach have tended to be somewhat obtuse.
- Eric Kandel and Antonio Damasio have noted the link and interwoven nature of a true biopsychosocial approach, such that psychiatric care does not belong to a separate and remote "psychological sphere" but also reflects and entails biological effects.
- In the same way, social components cannot be considered as completely distinct from biological and psychological domains.

Bragazzzi NL, 2013   Eid M, 2012

Categorical Approach

- It is very puzzling where to set the boundary between the "normal" (health status) and the "abnormal" (the disease) and this has not only academic and nosological issues, but above all social and political concerns.

- Another disadvantage of using the categorical approach alone is the nosological overlap: under the same clinical umbrella, different diseases with different prognosis can co-exist.

- Categorical approach, being qualitative, should be complemented with a more fine-grained diagnostic tool.

Bragazzzi NL, 2013

Kawa S et al 2012

Molecular Classification

- On the other hand, molecular classification can really help and improve the classical nosological taxonomy and thus ameliorate the outcome of patient management and care.

- This aspect of integrated psychological and biological assessment, that is to say both quantitative and qualitative, categorical and dimensional, is to be stressed within the frame of personalized medicine (P5) and targeted therapeutics, which recently emerged as promising and exciting trends.

OMICS Sciences

- According to etymology, OMICS is derived from the Sanskrit OM, which means "completeness and fullness".

- Thus, a holistic, systems-oriented approach, which may be well-positioned to fill the gap between the need for a rigorous and rational psychiatry and the need for a personalized medicine.

Bragazzzi NL, 2013

Ozdemir V et al, 2009

OMICS and Nosology

- By understanding the psychiatric diseases beyond their classic symptomatic or syndromal definitions using OMICS research, one can have a broader picture and unprecedented links and reclassification of psychiatric nosology.

The "Psychiatome"

- The interplay of genomics, proteomics, transcriptomics, toponomics, metabolomics and neuroimaging are emerging as powerful tools to analyze psychiatric disorders and provide patient's personalized care.
- Barabasi introduced the concept of "diseasome" in the context of network medicine.
- Goh et al. investigate the putative relationships among and between biological and environmental factors in psychiatric diseases, in what we call "psychiatome" (psycheomics), inspired by the concept of "diseasome".

Goh Kl et al, 2007

Meta-Structure Theory

- Instead of a classification based on clinical presentation (as in DSM-5, suggested ICD11), meta-structural taxonomy was proposed by Andrews and collaborators as based on risk factors and intended as a more parsimonious classification.

- The proposed clusters are: neuro-cognitive disorders (cluster 1), neuro-developmental disorders (cluster 2), psychoses (cluster 3), emotional disorders (cluster 4), externalizing disorders (cluster 5).

From Categorical Approaches to Dimensional Taxonomies: Endophenotype Theory

- The endophenotype makes use of biological markers, i.e., a biomarker or a biological trait as a measurable indicator of a disease, which may be or may not be causal
- The criteria for diagnosing an endophenotypic trait are:
1. It is associated with illness in the population.
2. It is heritable
3. It is disease state-independent;
4. Endophenotype and illness co-segregate within families.

Gottesman II et al, 2003

Why do we need manuals?

- Diagnosis

- Treatment

- Research

- Universal psychiatric language

What is Wrong with Manuals?

- Not culturally sensitive enough

- Does not take into account the very high co-morbidity of mental illnesses.

- Difficulties related to the research methodology leading to their development.

- The influence of Pharmaceutical companies in classificatory systems

What is Unique about Mental Illnesses that warrants Personalization?

- The ever changing nature of the brain along the life span
- The constant neural/environmental/cultural interaction (epistasis and epigenetics)
- The individualized behavioural/emotional presentation of psychiatric symptoms (behavioural markers).
- RDoC

Toward the Future of Psychiatric Diagnosis: Pillars of RDoC

National Institute of Mental Health Strategic Goal 1.4: Develop, for research purposes, new ways of classifying mental disorders based on dimensions of observable behavior and neurobiological measures

Aim #	Task
1	Initiate a process for bringing together experts in clinical and basic sciences to jointly identify the fundamental behavioral components that may span multiple disorders (e.g., executive functioning, affect regulation, person perception) and that are more amenable to neuroscience approaches.
2	Determine the full range of variation, from normal to abnormal, among the fundamental components to improve understanding of what is typical versus pathological.
3	Develop reliable and valid measures of these fundamental components of mental disorders for use in basic studies and in more clinical settings.
4	Integrate the fundamental genetic, neurobiological, behavioral, environmental, and experiential components that comprise these mental disorders.

Cuthbert B et al, 2013

Personalized P5 Medicine

- In the frame of the P5 medicine
1. Personalized
2. Participatory
3. Predictive
4. Preventive
5. Psycho-cognitive

They could establish links between psychiatric diseases, which are disorders with a final common symptomatology with vastly heterogeneous biological, environmental and sociological underpinnings.

Personalized Psychiatry

- A truly personalized psychiatry is a broader concept than simply of pharmacogenomics, genotyping or other molecular investigations: it also includes the cultural and spiritual beliefs and practices of the patient.

- This is particularly true also because from an evolutionary point of view, culture and genes have co-evolved such that culture can influence human genome , just as the expression of traits and actions arising from the genome can affect culture as pictorially.

Giordano J et al, 2005

Caspi A et al, 2006

Why can't we Totally Apply a Personalized Approach?

- The extreme Diversity and heterogeneity of the human experience.

- The wide variation in psychiatric training and background.

- Personal bias and possibility of malpractice.

Personalized Psychiatry;
is it the Future of our Profession?

- Advances in molecular genetics would help create a new individualized profiles for patients.

- This would have a profound effect on prevention and treatment.

- Targeting new and existing treatments more precisely to the patients most likely to benefit from them

- Use of digital markers instead of subjective checklists to monitor medical and environmental risk factors for mental illness.

Personalized Psychiatry Deserves Praise

- The goal of achieving personalized medicine in psychiatry is a laudable one (Deserving Praise), because its attainment should be associated with a marked reduction in morbidity and mortality.

- The goals of personalized medicine are to predict the individual's susceptibility to disease, achieve an accurate diagnosis, and result in an efficient and favorable response to treatment.

Mehta R et al, 2011   Myers AJ et al, 2010   Ozomaro U et al, 2013

Personalized Medicine

Ozomaro U et al, 2013

Indicators that the future is moving towards personalized psychiatry

Examples of suggested Neural Circuits in Psychiatric Disorder

- **Mood Disorder**:   LCSPT (Limbic- Cortical- Striatal-

     Pallidal- Thalamic Circuits)

- **OCD:**   Cortico- Striatal Circuit

- **Schizophrenia:**   CCTCC (Cortico-Cerebllar

     Thalamo-Cortical Circuit)

- **ADHD:**   Fronto-Striato Circuit

- **Autism:**   Heterogenous – Amygdala

- **Anorexia Nervosa:** Ventral and Dorsal neural circuits involving
     insula and striatal activity

- **PTSD:**   Middle frontal gyrus for further investigations.

Diffusion Tensor Imaging (DTI)

- It is an MRI-based neuroimaging technique which makes it possible to estimate the location, orientation, and anisotropy of the brain's **white matter tracts**.
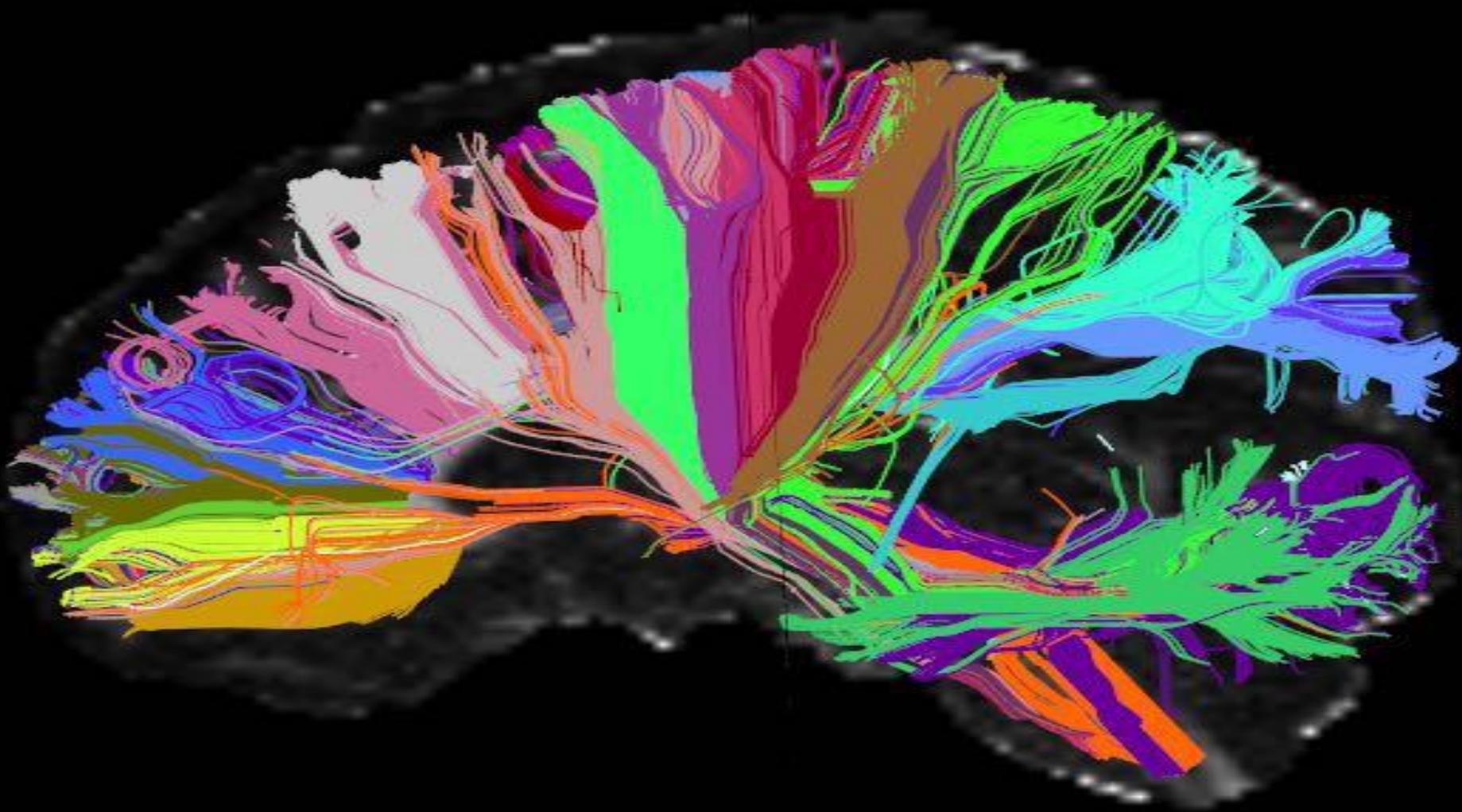
Fiber tracking

- Fiber tracking uses the diffusion tensor to track fibers along their whole length.

- In clinical practice, the most tracked fiber bundle is the cortico-spinal tract.

- However, fiber tracking can identify most of the brain's white matter tracts.
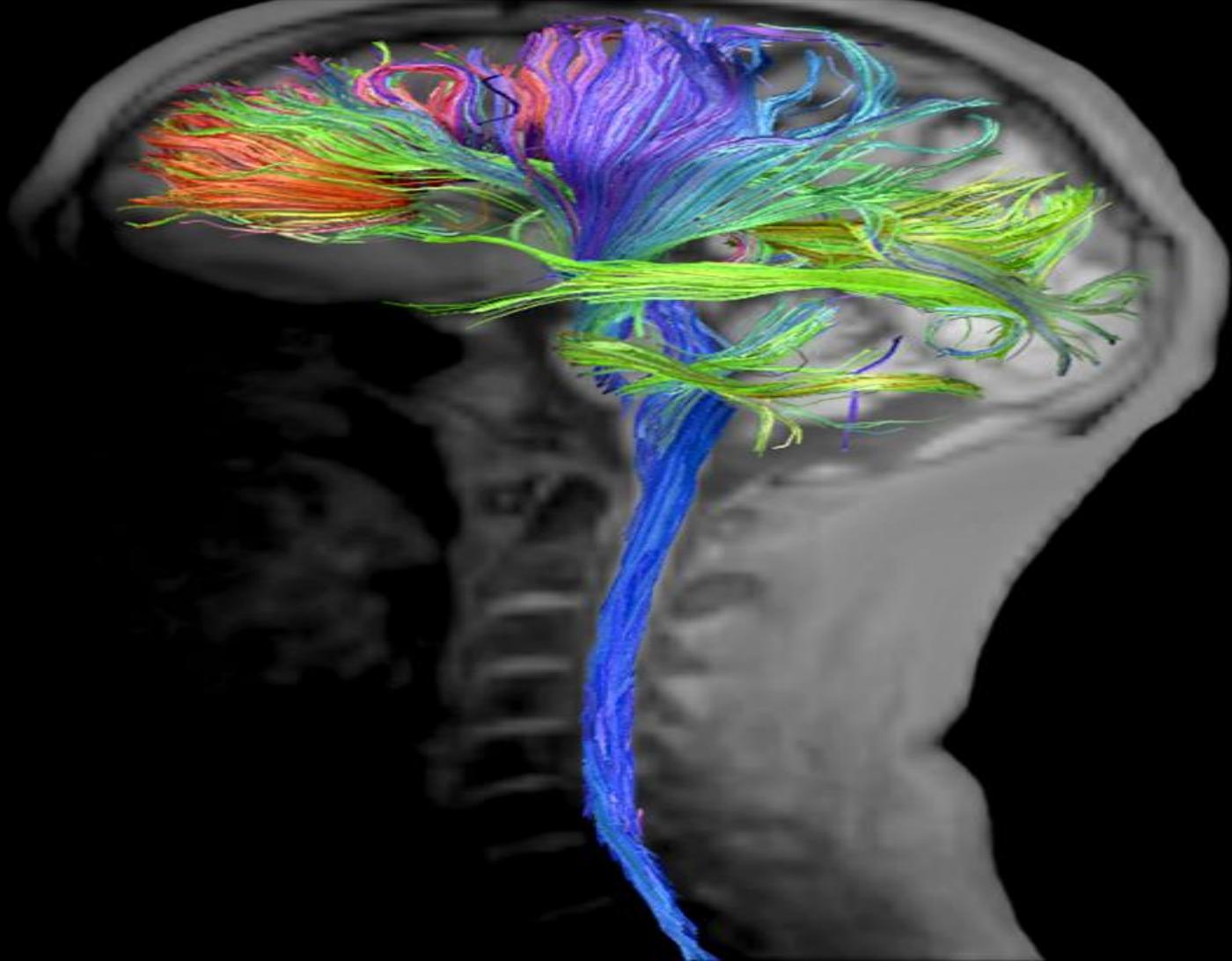
Human Connectome Project

- The Human Connectome Project aims to provide an unparalleled compilation of neural data, an interface to graphically navigate this data and the opportunity to achieve never before realized conclusions about the living human brain.
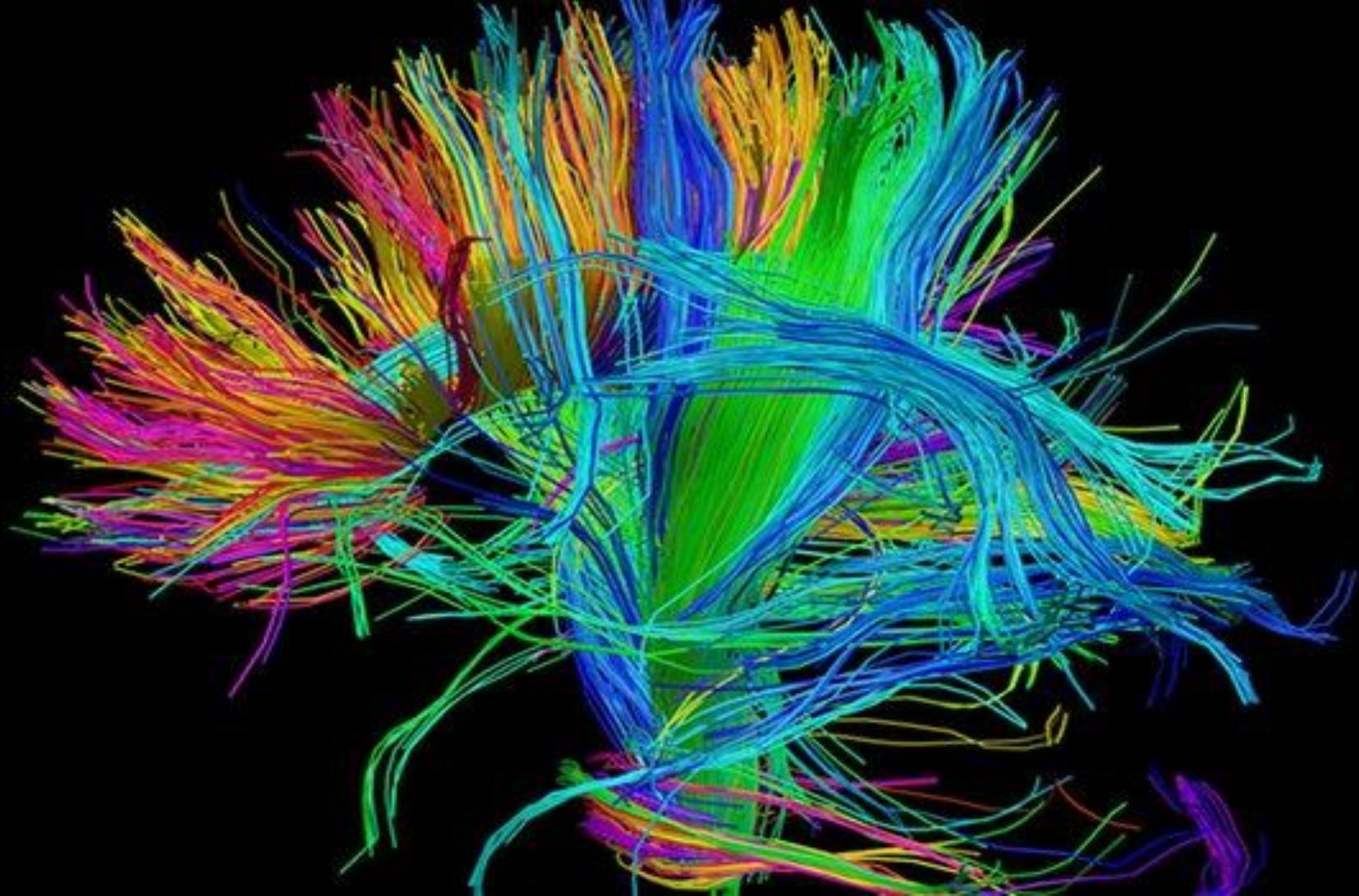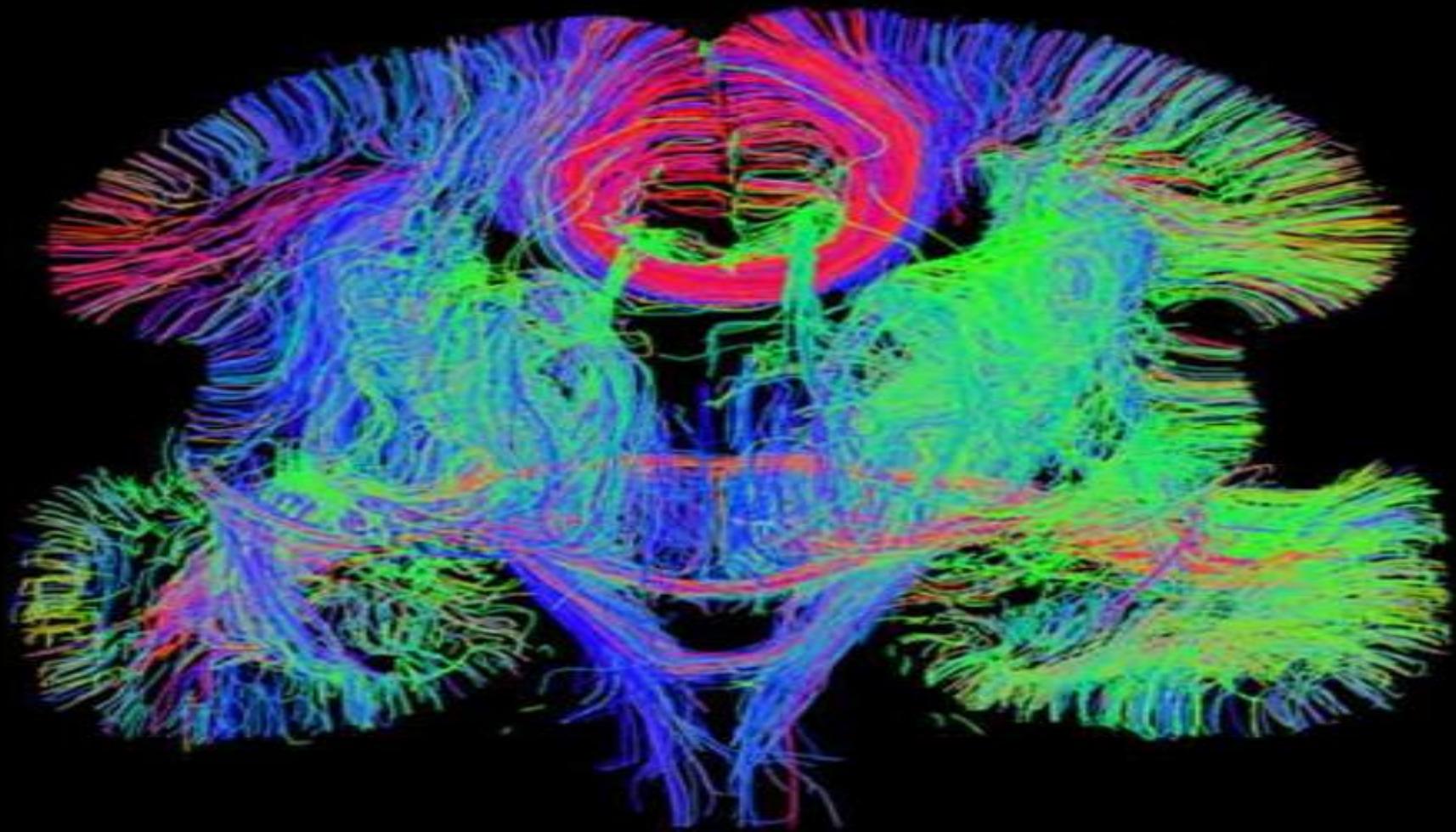
What is Pharmacogenomics?

- Pharmacogenomics is the study of the role of the genome in drug response. Its name (pharmaco- + genomics) reflects its combining of pharmacology and genomics.

- Pharmacogenomics analyzes how the genetic makeup of an individual affects his/her response to drugs

- It deals with the influence of acquired and inherited genetic variation on drug response in patients by correlating gene expression or single-nucleotide polymorphisms with pharmacokinetics (drug absorption, distribution, metabolism, and elimination) and pharmacodynamics (effects mediated through a drug's biological targets).

Pharmacogenomics

- The term pharmacogenomics is often used interchangeably with Phamacogenetics. Although both terms relate to drug response based on genetic influences, pharmacogenetics focuses on single drug-gene interactions, while pharmacogenomics encompasses a more genome-wide association approach, incorporating genomics and epigenetics while dealing with the effects of multiple genes on drug response.

Pharmacogenomics in Oncology

- To date, the field of oncology has seen the most success in leveraging the power of pharmacogenomics. Multiple gene-response associations have been discovered that are used to guide routine clinical practice for the selection of chemotherapeutic agents. Furthermore, across medical specialties, the Food and Drug Administration has approved commercially available tests that are purported to predict medication efficacy and toxicity, and a growing number of insurers are subsidizing some costs. Which is to say, in some fields, pharmacogenomics has arrived.

Hirschtritt etal., 2016

Pharmacogenomics

- In contrast, psychiatric pharmacogenomics is in its infancy; there are currently few validated and clinically useful gene-response associations that can be used to reliably guide psychotropic medication choice. Reasons that psychiatry may be lagging behind other specialties include the heterogeneity of psychiatric illnesses [e.g., DSM-based diagnoses may coincide more with general syndromes than distinct patho-physiologically based diseases], the lack of biomarkers for specific illnesses, and the difficulty in defining and standardizing clinical outcomes.

Hirschtritt etal., 2016

Pharmacogenomics in Psychiatry

- The best data for pharmacogenomic testing in psychiatry relates to the use of carbamazepine. As with many psychiatric medications, carbamazepine can have rare but dangerous adverse effects; in this case, Stevens-Johnson syndrome and toxic epidermal necrolysis. From a study of Taiwanese patients, the Food and Drug Administration now recommends that all patients of Asian descent be tested for a specific variant of the HLA-B gene before initiating therapy to avoid carbamazepine-induced Stevens-Johnson syndrome/toxic epidermal necrolysis.

Chen etal. 2011

Pharmacogenomics in Psychiatry

- one of the most challenging clinical situations is when a patient with treatment-refractory schizophrenia develops potentially life-threatening, severe neutropenia, also known as clozapine-induced agranulocytosis (CIA)/clozapine-induced granulocytopenia

- A pharmacogenomic test that could predict who is likely to develop CIAG (and/or who could be safely re-challenged with clozapine after the resolution of an episode of CIAG) would be an extraordinarily valuable tool

Verbelen M. & Lewis CM. 2015

Pharmacogenomics

- ***<u>Misconceptions: Separating Marketing from Science</u>***

- is common for these patients to believe that pharmacogenetics testing can identify the perfect drug for them—a truly tailored treatment. The future may indeed hold that promise, but that is not the current reality.

- Psychiatrists, pharmacists, and patients can learn a great deal from pharmacogenetics testing; however, that report will not magically reveal the ideal medicine for a specific patient

DelBello & Bentley, 2017

Pharmacogenomics

- ***Successes: How Pharmacogenetics Is Used in Psychiatry Today***

While fully personalized psychiatry is still in the future, many current applications exist for pharmacogenetics in psychiatry practice. One example that arises quite commonly is in the management of patients who require antipsychotic medications, particularly aripiprazole and risperidone. People who are poor cytochrome P450 2D6 (CYP2D6) metabolizers will typically have substantial increases in circulating drug concentrations and area under the curve (AUC) on these medications. Pharmacogenetic testing of CYP2D6 can help determine if the initial and target dosage of certain antipsychotics should be lowered (eg, halved).1 (Aripiprazole and risperidone are also excellent examples of potentially "red" medications that can be safely and effectively dose adjusted.)

Nano technology

- One nanometer is a billionth of a meter, or 10^{-9} of a meter. Here are a few illustrative examples:
- There are 25,400,000 nanometers in an inch
- A sheet of newspaper is about 100,000 nanometers thick
- If a marble were a nanometer, then one meter would be the size of the Earth
- Nanoscience and nanotechnology involve the ability to see and to control individual atoms and molecules. Everything on Earth is made up of atoms the food we eat, the clothes we wear, the buildings and houses we live in, and our own bodies.

Nano medicine

- Nanomedicine is defined as the area using nanotechnology's concepts for the benefit of human beings' health and well being.

Fond etal., 2013

Nano- Psychiatry

- The main applications of nanotechnology in psychiatry are:

1) Pharmacology

There are two main difficulties in neuropharmacology: drugs have to pass the blood-brain barrier and then to be internalized by targeted cells. Nanoparticles could increase drugs bioavailability and pharmacokinetics, especially improving safety and efficacy of psychotropic drugs.

Fond etal., 2013

Nano- Psychiatry

2) Living analysis

Nanotechnology provides technical assistance to in vivo imaging or metabolome analysis

Nanotechnology will aid psychiatrists and neurologists as an advanced diagnostic (or neuroimaging) tool, assessing brain activity in greater detail than ever before.
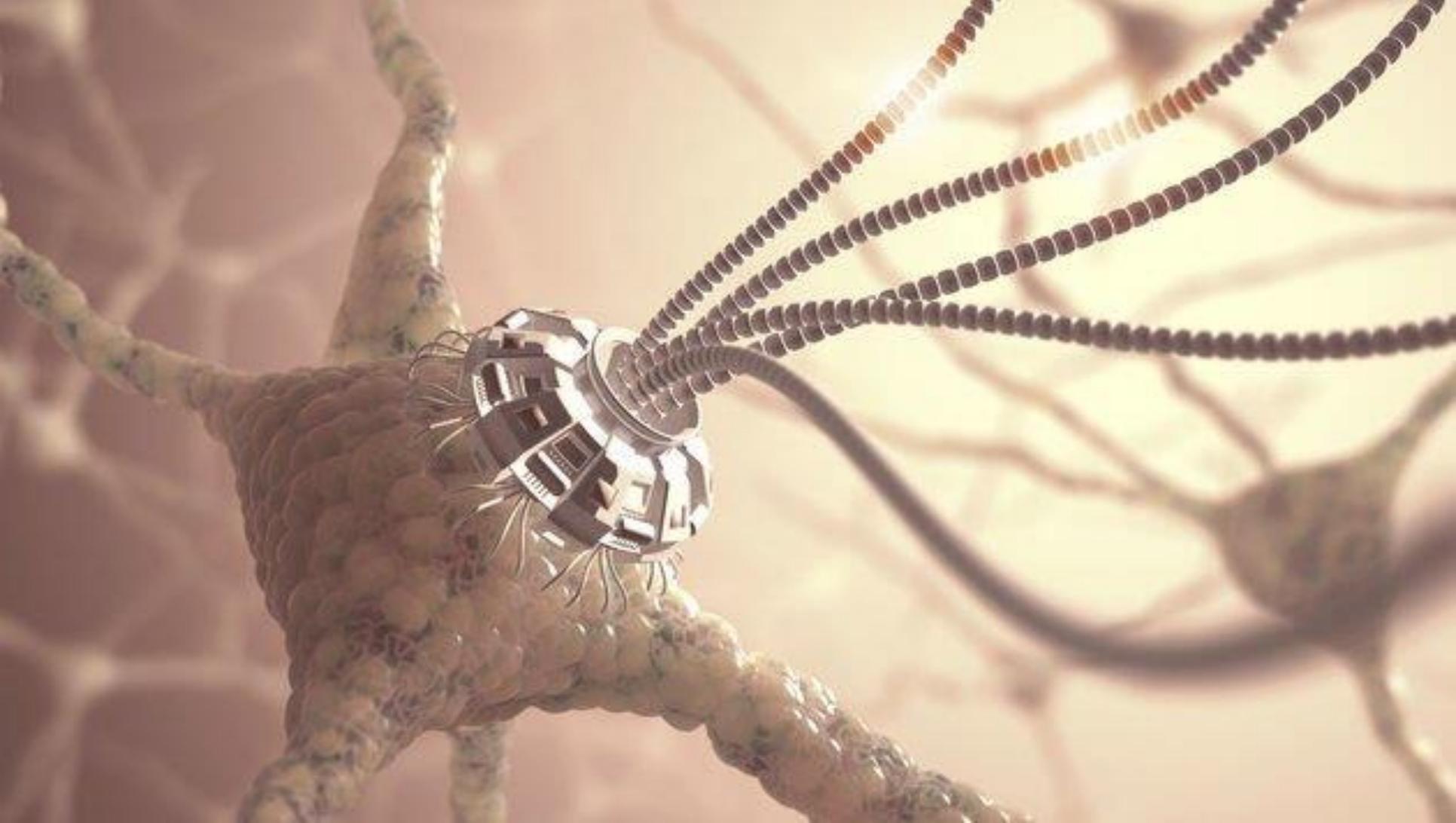
Nano- Psychiatry

3) Central Nervous System Modeling

Research teams have succeeded to modelize inorganic synapses and mimick synaptic behavior, a step essential for further creation of artificial neural systems. Some nanoparticle assemblies present the same small worlds and free-scale networks architecture as cortical neural networks. Nanotechnologies and quantum physics could be used to create models of artificial intelligence and mental illnesses.
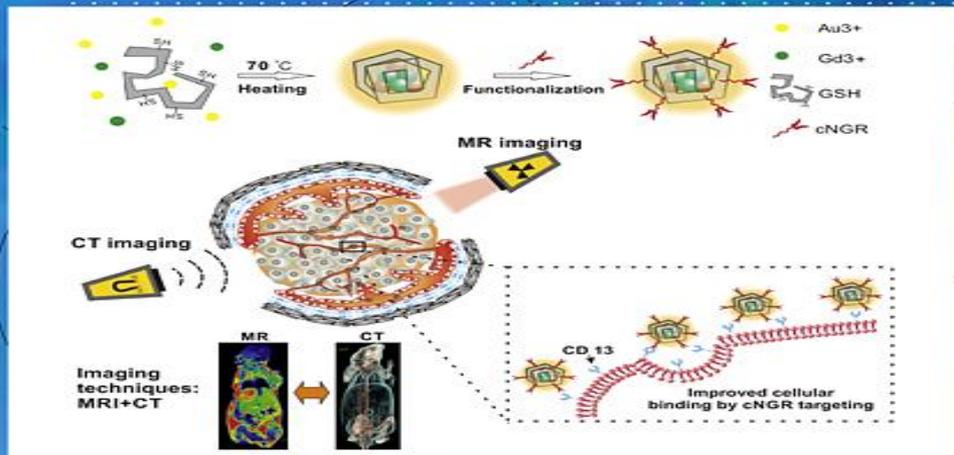
Nano- Psychiatry

- Advances in nanobiotechnology will facilitate the development of personalized medicine by: (1) Nanodiagnostics will improve the sensitivity and extend the present limits of molecular diagnostics, point-of-care devices, biochips and biosensors; (2) improve discovery of biomarkers; (3) facilitate integration of diagnosis and therapy, which is an important part personalized medicine; and (4) nanomedicines are suitable for targeted delivery to lesions.

Jain, 2018

nanomedicine
Nanotechnology., Biology., and Medicine

- Au3+
- Gd3+
- GSH
- cNGR

70 °C Heating

Functionalization

MR imaging

CT imaging

CD 13

Improved cellular binding by cNGR targeting

Imaging techniques: MRI+CT

MR

CT

X. Li, M. Wu, J. Wang, Y. Dou, X. Gong, Y. Liu, Q. Guo, X. Zhang, J. Chang, Y. Niu

Ethical Problems

- Assuming nanotechnology can be used to treat mental illness, who's to say that it can't also be used to augment a person's natural capacity?

- What if a person doesn't have a mental illness, but wants to feel even happier?

- What if the usage of nanotechnology alters a person's core personality or has long-lasting unwanted consequences?

- It is important to consider ethical restraints that may be imposed upon nanotech being used to target the brain.

Conclusions (1)

- Further studies must be undertaken to better characterize the relationships between genes, culture, and environment, but we hold that a P5-based psychiatry can uphold these tasks.

- Currently integrating both approaches is the best, until personalized psychiatry becomes a reality or manualized psychiatry becomes personalized!!!

Conclusions (2)

- Perhaps the "psychiatome" will provide an adequate translational framework for both psychiatric research and practice, being holistic and broad, rather than narrow and simplistic, even though this promising paradigm, at present, is still at an early stage of its development and implementation.

- Nanomedicine is in its early days and even earlier for nanopsychiatry, and we are still far from seeing a practical application in daily psychiatric practice.

- It seems important, however, that psychiatrists do not forsake this area of research the promises of which could be decisive in the field of mental illness.