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Translational Biomedicine and Dichotomous Correlations of Masking

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Abstract

A hierarchically organized system is based on the predictive coding model of neural function in which a primary purpose of neural interactions is to minimize prediction error by masking. Neural data suggests that this is not a simple continuum and that non-clinical odd beliefs may be mediated by a striatal system which is distinct from the cause of pathological delusions in right frontal cortex. In psychotic subjects it was referred on so called “divided Self”, which are interpreting themselves as a machine or robot, not clear as humans. The goal of translational medicine (TM) is to combine disciplines, resources, expertise, and techniques within these pillars to promote enhancements in prevention, diagnosis, and therapies. Accordingly, TM is a highly interdisciplinary field, the primary goal of which is to coalesce assets of various natures within the individual pillars in order to improve the global healthcare system significantly. It results in general knowledge and understanding of nature and its laws.

Keywords: The predictive coding; Prospect-masking; New biology; Human predators; Robots; The real self

Translational Biomedicine and Phenomena of Masking

Translational biomedicine-TM is defined by the European society for translational medicine (EUSTM) as an interdisciplinary branch of the biomedical field supported by three main pillars: benchside, bedside and community. Translational research is broken down into five levels, T1 through to T5. T1 research, refers to the “bench-to-bedside” enterprise of translating knowledge from the basic sciences into the development of new treatments; and T2 research refers to translating the findings from clinical trials into everyday practice [1].

Translational research includes two areas of translation. One is the process of applying discoveries generated during research in the laboratory, and in preclinical studies, to the development of trials and studies in humans. The second area of translation concerns research aimed at enhancing the adoption of best practices in the community. Cost-effectiveness of prevention and treatment strategies is also an important part of translational science.

Basic research is the systematic study directed toward greater knowledge and understanding of the fundamental aspects of phenomena, and is performed without thought of practical ends. It results in general knowledge and understanding of nature and its laws.

Applied research is a form of systematic inquiry involving the practical application of science. It accesses and uses some part of the research communities (the academia‘s) accumulated theories, knowledge, methods, and techniques, for a specific, often state, business, or client-driven purpose. In medicine, translational research is increasingly a separate research field. A citation pattern between the applied and basic sides in cancer research appeared around 2000.

Given the our previous observations concerning patients with first episode psychosis show altered neural responses to prediction error (PE). This alteration in turn relates to the severity of their delusional ideation, results provide novel evidence for view that schizotypy relates to psychosis at more than just a superficial descriptive level. Healthy unusual ideas have their source in aberrant striatal functioning. They may find this personally, socially and even financially advantageous. A striatal system capable of entertaining irrelevant associations is not detrimental given the link between creativity and healthy schizotypy (generate novel or unusual associations). A deficit in belief evaluation is associated with right frontal cortex dysfunction.

In blocking prior learning leads to an attenuation of new learning because of subsequently reduced expectation that a blocked stimulus has a predictive power. An inappropriate dorsolateral prefrontal (DLPFC) PE signal during causal learning in subjects with psychosis was predictive of the severity of delusions. It’s an evidence that aberrant right frontal PE signal relates to schizotypy. The severity of subject’s baseline magical ideation is correlated negatively with magnitude of their striatal PE response to the blocked cue. People with highest degrees of distress showed least PE response to violation of blocking-induced expectation in frontal cortex. Subjects with inappropriate DLPFC response during blocking trials were most distressed by their odd beliefs and not the reality.

Neurobiological Correlates of Prospect-Masking

Translational medicine is a rapidly growing discipline in biomedical research and aims to expedite the discovery of new diagnostic tools and treatments by using a multi-disciplinary, highly collaborative, "bench-to-bedside" approach. The question is if our experience of reality is accurate or is a fiction? For these fascinating processes F. Crick and Ch. Koch coined a term: neuronal correlates of consciousness (NCCs). Given that the processing time of lone neurons is in the millisecond range, this categorization is remarkably swift and can be accomplished only via massive parallel processing. Our perceptions lag behind reality, casting doubt on our presumed unity of consciousness. For example, when stimuli follow in rapid succession, registering one image can distort previous or subsequent images or suppress them completely. Psychologists refer to this effect as masking.

Masking makes it clear that our perception can deviate significantly from reality. Such systematic distortions of perception teach us the rules that the mind uses to construct its view of the world. The most used technique is backward masking, in which the mask follows an initial stimulus. Both stimuli can fuse completely. Two images in rapid succession result in a single conscious impression. Masking can eliminate conscious recognition, while only the input stages of the visual brain were activated. This means that even an image that strikes the retina one tenth of a second after a prior image can cancel out conscious perception of the first image. The masking thwarts the development of a visual impression, it cannot prevent unconscious processing: it had been masked from conscious perception.

As soon as neuronal signals within the visual cortex or between the cortex and deeper brain regions start shuttling back and forth, as they do, subsequent information can distort the processing of earlier information. Our perceptions lag considerably behind reality and we don't notice that. In all probability, subsequent brain activity during backward masking disturbs precisely those processes that signal the onset and disappearance of a target stimulus. This competition among overlapping neural coalitions are a significant feature of the censorship in a consciousness.

If sensing such a simple input can be so variable, imagine how complicated it must be for the brain to assess the actual world. How do we integrate all these details into a unified image that conveys a person's identity, gender and emotional state? This question goes to the core of the so-called binding problem. If NCCs arise within the various processing centers in the brain at different times, shouldn't each of the attributes be perceived with a time lag? The answer may be given by the mechanism of dependence length minimisation (DLM). (Gibson et al. 2015) A unified impression is rapidly reached because the brain has no mechanism for registering the asynchrony. [2].

We simply perceive all the qualities of an object simultaneously–as incoherent as that composite image might be. It means that continuity of consciousness may be yet another illusion. Consider patients who experience "cinematographic vision". They lose their sense of visual continuity and instead see a flickering series of still images. The images do not overlap or seem superimposed, they just last too long, like a movie that has been stuck on freeze frame and then suddenly jumps ahead to catch up to a real-time moving scene.

Our perception seems to be the result of a sequence of individual snapshots, a sequence of moments, like individual, discrete movie frames that quickly scrolling past us, we experience as continuous motion. We experience events at the same moment as synchronous, that reach us sequentially and are perceived in that order. The duration of such snapshots is between 20–200 milliseconds. If the individual images were shorter in duration–there were more of them per unit of time–then time would appear to pass more slowly. People who have been in automobile accidents, natural catastrophes and other traumatic events often report that at the height of drama, everything seemed to go in slow motion ("time dilation"). It is a question of how the brain mediates our sense of time. In fact, changing coalitions of larger neuron groups are the neuronal correlates of consciousness which is generating our flow of consciousness.

Accommodating and Deceiving Others

The term "dichotomous" we are using as meaning of "twofaced", i.e. as something that has it's good face and also it's bad face at the same time. Between basic authors on the topics of the masking we can name psychiatrist R. D. Laing with his first book titled The Divided Self. The dilemma of the divided self is that the more isolated "the real self" becomes, the less equipped it is to contend with reality and ordinary developmental processes. Moreover, "the false self" becomes increasingly identified with the publicly observable body, and the real self with person's invisible mind. As mind and body become more split, the real self becomes more volatile, disembodied, accommodating and/or deceiving others. This schizoid and psychotic potential than can be used during masking unfairly for one's own advantage [3].

Default-Mode Network

In the hierarchical architecture a secondary process provides top-down predictions to reduce free-energy associated with the Freudian primary process, which is converting free energy into bound energy. In both accounts, higher cortical areas are trying to organize activity in lower-levels through suppression of their energy. The so called default-mode network (DMN) is a network of regions that show high metabolic activity (glucose metabolism, oxygen consumption) and blood flow at rest but which deactivate during goal-directed cognition [4]

The medial prefrontal cortex sends dense projections to the ventral striatum and midbrain. The ventral striatum displays functional connectivity with the midbrain, medial temporal lobes and higher-level nodes of the DMN and the midbrain and ventral striatum signal prediction error and motivational-

salience. The attention system is activated during externally-directed cognition and deactivated during internally-directed cognition, while the opposite is true of the DMN. Much of the brain's vast energy budget is reserved for spontaneous neuronal activity. Spontaneous activity in the DMN reflects the constant containment of spontaneous endogenous activity. The spontaneous activity in the dorsal attention system indexes the continual monitoring and suppression of exogenous stimuli [5].

Based on empirical findings it was proposed that bursts of limbic theta recorded in the cortex as increased gamma may index the positive symptoms of various neurologic and psychiatric disorders. These findings imply that theta modulates coupling between theta and gamma and theta can promote long-range coupling in cortical networks. A retreat from the external world is characteristic of a loss of an intense object-love. The patient reacts to this loss by targeting the aggression felt the lost object back upon his/her own ego. A reduced task-induced suppression of DMN activity is related to reduced blood flow and activation in the dorsolateral prefrontal cortex, hyper-perfusion, metabolism and activity in limbic and medial prefrontal regions.

Geniality Means Anti-Predatory

Within public health, translational medicine is focused on ensuring that proven strategies for disease treatment and prevention are actually implemented within the community. When a scene hits the cones (color receptors) in the eye, neural signals from the retina travel to the area 17, in the occipital lobe at the back of the brain. There the image is processed further within local clusters. Afterward, the information is sent forward and distributed to several regions in the temporal and parietal lobes. In the case of color, the information goes to area V4 in the fusiform gyrus of the temporal lobe. From there it travels to areas farther up in the hierarchy of color centers, including a region near a patch of cortex called the TPO (for the junctions of the temporal, parietal and occipital lobes).

Abstract, numerical computations happen in stages. An early step also take place in the fusiform gyrus, where the actual shapes of numbers are represented. Later one occurs in the angular gyrus, a part of the TPO concerned with numerical concepts (ordinality: sequence, cardinality: quantity). Brain-imaging studies in humans suggests that visually presented letters or numbers activate cells in the fusiform gyrus, while the sounds are processed higher up in the TPO. The number-color synesthesia is caused by cross-wiring between V4 and the number appearance area (both within the fusiform) or between the higher color area and the number-concept area (both in the TPO) [6].

The processes of cross-linking in TPO is showing its potentially important role during generating the level of human creativity and geniality.

The neurological basis of synesthesia could help explain one skill that many creative people share facility for using metaphor to make links between seemingly unrelated domains. Metaphor involves making links between seemingly unrelated conceptual realms, while this is not just a coincidence. Coincidence is at a deeper level a manifestation of entanglement entropy [7] Mutation of the angular gyrus make possible for synesthesia to provide excess communication among different brain maps. Involved in cross-modal synthesis the brain regions where information from touch, hearing and vision flow together are enabling the construction of high-level perceptions. The angular gyrus is disproportionately larger in humans than in apes and monkeys–evolved originally for cross-modal associations. Probably later became co-opted for more abstract functions such as metaphors [6].

The common abstract property is extracted somewhere in the vicinity of the TPO, probably in the angular gyrus. It is extracting the abstraction of the common denominator ("ratio") from a set of strikingly dissimilar entities. When the ability to engage in cross-modal abstraction emerged, it is opening the way for more complex types of abstraction–i.e. for geniality of thinking.

Nonlinear Deviation Term: Geniality

Neurobiological correlates of value have been described in orbitofrontal (conscience), cingulated cortex (critical intellectuals) and the basal ganglia, areas of the brain traditionally associated with reward-seeking behavior.

Some neurons in orbitofrontal cortex represent value independently from evidence, choice and action. Anterior cingulate cortex is thought to represent negative (critical, non-linear) value [8,9].

There is much evidence that a number of brain regions are sensitive to expected reward (or "utility"). The most well established are dopaminergic regions such as the striatum and midbrain structures. The common ratio pattern can be reconciled by the plausible assumption that people apply nonlinear decision weights $\pi(p)$ to objective probabilities$p$, so that the ratio $\pi(0.02)/\pi(0.01)$ is much smaller than $\pi(1)/\pi(0.5)$. Neural responses to probabilities resembling the smoothly increasing function which typically fit behavior well. Paulus and Franck [8] focused on between subjects measures and showed that activity in anterior cingulate correlated with degree of nonlinearity across subjects. We can make the assumption that neural activity is approximately a linear function of the behaviorally derived utility function. The GLM model separates the weighting function into two components: (1) component that is linear in $p$and (2) the component that is the nonlinear deviation term (NDT) $\Delta(p,\alpha_i) = \pi(p,\alpha_i) - p$. Specifically, we are looking for a prospect-theoretic expected value function that is nonlinear in p; that is $\pi(p,\alpha)u(x) = p \cdot u(x) + \Delta(p,\alpha) \cdot u(x)$. We assume the function $(x)$is power function x^p, where the value of $p$is taken from the individual behavioral estimate, and $\Delta(p,\alpha_i) = \pi(p,\alpha_i) - p$, where the mean group α= 0.771 is used.If the expected utility (EU) null hypothesis is an accurate approximation of valuation of risky choices, there should be no

reward-related brain regions that respond to the deviation term $\Delta(p,\alpha)\cdot u(x)$. If the nonlinear weighting hypothesis is an accurate approximation, there should be reward-related brain regions that respond equally strongly to the linear component $p\cdot u(x)$ and to the nonlinear component $\Delta(p,\alpha)\cdot u(x)$. We can test whether cross-subject variation in the inflection of nonlinear weighting inferred from choices is consistent with cross-subject differences in neural activity. More highly nonlinear functions will be approximated by a combination of the linear term p and the nonlinear term $\Delta(p,\alpha_i)=\pi(p,\alpha_i)-p$ that puts more weight on the nonlinear term. A linear-weighting subject, will put no weight on nonlinear deviation $\Delta(p,\alpha_i)=\pi(p,\alpha_i)-p$. Denote the true weighting function for subject i by $\pi(p,\alpha_i)$, and the deviation from linear weighting by $\Delta(p,\alpha_i)=\pi(p,\alpha_i)-p$. A brain region that represents $\pi(p,\alpha_i)$ will be significantly correlated with both $\Delta(p,\alpha_i)$ and p. That is, the linear term p and nonlinear deviation term with a higher weight on the nonlinear deviation term [10]. Brain regions that are significantly correlated with the nonlinear term include the anterior cingulated cortex (ACC), the striatum, motor cortex, and cerebellum. Our intuition is that brain activity during valuation of risks is more likely to correspond to cognitive components of prospect-masking, than to EU, and it will be easier to construct an adaptationist account of how evolution would have shaped brains to follow prospect-masking rather than EU. The prospect-masking follows from psychophysics, while EU from normative logic.

As a biological illustration of the subject with genial NDT we can propose Nobelist John Forbes Nash. He had new genial ideas, and later it has mentioned in his Nobel autobiography, because of “deviated somewhat from the line”.

More exact definition of geniality is giving Robert Sternberg. On the top of that genius requires a combination of high motivation personality factors such as openness to experience, immense amounts of learning, at least ten years immersed in one’s discipline and environment that fits the potential genius like a glove. Many highly creative individuals lost a parent when they were young. This gives them an independent drive that might not have occurred otherwise.

The increased specialization required today for professional credentials makes the broad thinking of that characterizes geniuses harder to develop. I agree that the ritual culture of academia may also hamper genius. As philosopher of science Thomas Kuhn has pointed out, highly creative work (without precedent) does not fit existing formalistic academic paradigms tend to be dismissed (the counter-selection) [11]. Many great scientists have related how their most original ideas were repeatedly rejected by their peers.

The most productive environment for the formation of new ideas is one that encourages networks of minds operating in a non-market setting. For example, creative contributions that incrementally advance existing knowledge differ in their impact from those that redirect a field. The former are rewarded by a field’s referees and editors, the latter may be accepted only grudgingly, if at all, because they challenges the conventional wisdom. Inventive people also tend to be crowd-defiers. Creative people are thus intellectually combative.

A working environment that encourages creativity must tolerate and even encourage such contrariness. It must also recognize that the more creative an idea is, the harder it will be to sell. Reviewers of grant proposals and journal articles must recognize that highly creative research may be less developed than that which only furthers established paradigms, and should make more allowances for originality [12].

Dichotomous Correlations of Adaptation

One prevalent description of translational medicine, first introduced by the Institute of Medicine's Clinical Research Roundtable, highlights two roadblocks (i.e., distinct areas in need of improvement): the first translational block (T1) prevents basic research findings from being tested in a clinical setting; the second translational block (T2) prevents proven interventions from becoming standard practice.

An important role in the processes of adaptation and masking in humans is playing also the immune system. The innate immune system functions as an interpreter of tissue damage and provides a first line of defense, also translates the information to other repair and defense systems in the body by stimulating angiogenesis, wound repair, and activating adaptive immunity. It is appropriate to consider autophagy a means for programmed cell survival balancing and counter-regulating apoptosis. Autophagy seems to have a dichotomous role in tumorigenesis and tumor progression.

Two other attributes play a similarly paradox role. The first involves major reprogramming of cellular energy metabolism in order to support continuous cell growth and proliferation replacing the metabolic program that operates in most normal tissues. The second involves active evasion by cancer cells from attack and elimination by immune cells. This capability highlights the dichotomous correlations of an immune system that both antagonizes and enhances tumor development and progression.

Evidence began to accumulate in the late 1990s confirming that the infiltration of neoplastic tissues by cells of the immune system serves counter-intuitively to promote tumor progression [13,14].

The Twofaced New Main Law of Nature

The quantum entanglement is a basis of twofaced reality in which we are living our lives. From this reality are outgoing also the science and healthcare too. Although metastasis is important for systemic correlations expansion (as in tumors), it is a highly dichotomous process, with millions of cells being required to disseminate to allow for the selection of cells-

correlates aggressive enough to survive the metastatic cascade. To quantify the dynamics of metastasis of correlations development, we need look at the incidence of metastases in terms of co-occurrence at every point of time. To quantify co-occurrence we can use the ϕ-correlation between dichotomous variables defined as: $\frac{N_X(t)C_{ij}(t) - m_i(t)m_j(t)}{\sqrt{m_i(t)m_j(t)\left[N_X(t) - m_i(t)\right]\left[N_X(t) - m_j(t)\right]}}$ where $C_{ij}(t)$ is the number of co-occurrence at time t. Than i and j represent particular site of metastasis, X represents the primary correlations type. The pair-wise correlations between metastasis network links for every primary correlations types and lead to the correlation coefficient matrix.

The dichotomous correlations of the adaptation may be caused also by the Quantum Entanglement Relative Entropy as a measure of distinguishability between two quantum states in the same Hilbert space. The relative entropy of two density matrices$p_0$and$p_1$is defined as $S(p_1|p_0) = tr(p_1 \log p_1) - tr(p_1 \log p_0)$. When p_0 and p_1 are reduced density matrices on a spatial domain D for two states of a quantum field theory (QFT), implies that $S(p_1|p_0)$ increases with the size of D. Than $\Delta S_{EE} = -tr(p_1 \log p_1) + tr(p_0 \log p_0)$ is the change in entanglement entropy across D as one goes between the states.When the states umder comparison are close, the positivity is saturated to leading order: $S(p_1|p_0) = \Delta \langle H_{\mathrm{mod}} \rangle - \Delta S_{EE} = 0$.

The problem of conventional adaptation may be given by a definition of static, deterministic world. The proliferative correlations lead to the resonances between the degrees of freedom. When we increase the value of energy, we increase the regions where randomness prevails. For some critical value of energy, chaos appears: over time we observe the exponential divergence of neighboring trajectories. For fully developed chaos, the cloud of points generated by a trajectory leads to diffusion [15]. Here we must as first formulate a new main natural law: the quantum entanglement entropy (QEE) [11]. Through above resonances the QEE is causing a metastasis of correlations, antagonistically intertwining all types of potentially conflicting interests.

Focus on Cross-Functional Collaborations

The national institutes of health (NIH) has made a major push to fund translational medicine, especially within biomedical research, with a focus on cross-functional collaborations (e.g., between researchers and clinicians); leveraging new technology and data analysis tools; and increasing the speed at which new treatments reach patients.

Another masked problem of dichotomous correlations in cancer arose from conflicting effects of E-cadherin and p120, adhesion proteins that are essential for normal epithelial tissues to form, and which have long been considered to be tumor suppressors. New study has found that this hypothesis didn't seem to be true, since both E-cadherin and p120 are still present in tumor cells and required for their progression. That led researchers to believe that these molecules have two faces: a good one, maintaining the normal behavior of the cells, and a bad one, that drives tumorigenesis. It uncovers a new strategy for cancer therapy [16]. This finding represents an unexpected New Biology that provides the code, the software for turning off cancer.

An another new research estimates that ocean fishing has resulted in humans exploiting adult fish populations at about 14 times the rate of other marine predators, while humans have hunted and killed adult land animals at round nine times the rate of other animal predators [17].

Human hunting and fishing has had an extraordinary impact on the natural world and its ruthless efficiency is laid bare in detailed survey of 2,125 species of terrestrial and marine predators around the world. The study revealed that human hunting and fishing is qualitatively different to the predatory behavior shown by other species. It has, concentrated on killing mature adult animals rather than their offspring, which the scientists have likened to eating into the reproductive capital rather than the reproductive interest of the natural world.

Whereas predators primarily target the juveniles i.e. reproductive interest of populations, humans draw down the reproductive capital i.e. exploiting adult prey. The study found that humans have fundamentally changed the balance of marine ecosystems [17].

Our wickedly efficient killing technology, global economic systems, and resource management that prioritize short-term benefits to humanity have given rise to the human super-predator. Our impacts are as extreme as our behavior and the planet Earth bears the burden of our predatory dominance. In fact, the sustainable exploitation paradigm management is typical for all global activities of humans. Humans by above over-exploitation have altered course of evolution.

But what is masking this super-predatory behavior of humans? Brain mechanisms involved in predatory aggression activated in violent intra- and extra- specific aggression are very similar. Unemotional violence associated with antisocial personality disorder is called predatory because it involves restricted intention signaling and low emotional/physiological arousal, including decreased glucocorticoid production. This epithet is covering a structural similarity at the level of the hypothalamus where the control of affective and predatory aggressions diverges.

Aggressive encounters activate the mediobasal hypothalamus, a region involved in intra-specific aggression. The activation of the lateral hypothalamus is involved in predatory aggression. Glucocorticoid deficiency increased activation in the central amygdala, also involved in predatory aggression. In addition, activation patterns in the periaqueductal gray – involved in autonomic control is also seen in predatory aggression. The above findings suggest that

antisocial and predatory aggression are not only similar, but are controlled by overlapping neural mechanisms.

Conclusions

In December 2011, the national center for advancing translational science (NCATS) was established within the NIH to "transform the translational science process so that new treatments and cures for disease can be delivered to patients faster." Establishing a neural and evolutionary basis of prospect-masking can show how the foundation for principles guiding social science might be usefully shifted from relying largely on logic, to respecting biological implementation. It may include convergence to logical principles as a result of learning or higher-order cognition.

So called prior probability affects the threshold for initiating an action. Priors can be manipulated by changing the probability of the target which is shown to the right or left fixation.

Differences in the distribution of reaction time for different priors conformed to the “swivel” prediction, suggesting a change in the threshold and in the rate of rise of decision variable (DV). The threshold appeared to change as a linear function of the logarithm of the prior, which is suggesting that the DV has units log (P). This implies a form of probabilistic reasoning, with the DV representing a level of certainty that the prepared movement should be executed.

Further studies have shown that different decision strategies that favor urgency, certainty, or prior expectations seem to trade off in these units of log (P) [9].

Even more important, there exists a multiplicity of evolutions, which are particularly evident in the field of biology. As stated by Stephen J. Gould, bacteria have remained basically the same since the Precambrian era, while other species have evolved dramatically, often over short time scales. It would therefore be a mistake to consider a simple one-dimensional evolution. Some two hundred million years ago, certain reptiles started to fly, while others remained on earth. At a later stage, certain mammals returned to the sea, while others remained on land. Similarly, certain apes evolved into humanoids, while others did not.

At the conclusion it is appropriate to cite Gould’s definition of the historical character of life: To understand the events and generalities of life’s pathway, we must go beyond principles of evolutionary theory to a paleontological examination of the contingent pattern of life’s history on our plane–the single actualized version among millions of plausible alternatives that happened not to occur.

Such a view of life’s history is highly contrary both to conventional deterministic models of Western science and to the deepest social traditions and psychological hopes of Western cultures for a history culminating in humans as life’s highest expression and intended planetary steward [15].

Humans are a unique super-predator that hunts and kills other species many times more efficiently than other top predators both on land and sea [17].

Masking means that what you know isn’t what you know. A new theory has suggested that our entire lives and memories are maybe not real, instead being part of a computer programme played by advanced robots.

In 2007-2013 the European Commission targeted a majority of its €6 billion budget for health research to further translational medicine [1].

The Clinical and Translational Science Awards, established in 2006 and now funded by NCATS, supports 60 centers across the country that provide "academic homes for translational sciences and supporting research resources needed by local and national research communities."

Conflict of Interest Disclosure

The author declares no conflict of interests.

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