Envisioning the Future of Neuropharmacology Applying the Arts & Sciences

Exploring novel uses of fine art to spark ideas and innovations in Pharmacology

Introduction

Pharmacology, which marks its 19th century origins with the work of synthetic organic chemist Friedrich Wohler, promises a rich future in the evolution of drug discovery, development and medical applications that impact human health and wellness. Understanding the physiological activity and therapeutic effects of chemical compounds on human systems remains a concerted collaborative effort of pharmacologists considering the combined empirical studies by neuropsychologists, neuropharmacologists, toxicologists, microbiologists, clinicians, and many other specialists whose work informs drug design and therapy.

This article explores some arts-based methods of learning that foster creative inquiry, discovery, problem-solving, and innovative thinking that may be useful for neuropharmacologists who aim to advance knowledge of how drugs interact with the body (pharmacodynamics) and vice versa (pharmacokinetics): from drugs known to affect the actions of enzymes and cell-receptors to biochemical changes in cell/neurons that reveal the body's response to various medicinal packages. Indeed, there's a "fine art" to Pharmaceutical Sciences that can catalyze vital innovations leading to new treatments for preventing common illnesses and uncommon diseases.

The visual arts offer many versatile tools and methods that can inspire innovative thinking in Neuropharmacology, which provides practical insights into the unsolved mysteries of how drugs influence the human brain and body it governs. The author presents a selection of metaphorical artworks he created that can be used to pose fresh questions about the ways in which drugs affect everything from genes to proteins to networks of neural tissue to affective and cognitive processes to intentional actions and behaviors.

The nine exploratory artworks embody, express and explore aesthetic experiences that reflect brain activities; specifically, those involved in processing our primary emotions (anger, sadness, disgust, pleasure, fear and anxiety), and the impact they have on human nervous systems (LeDoux, 2012). Although countless rational people believe "higher-order" cognitive functions control our "lower-order" affective functions, the turbulent state of the world today and visible expressions of our anxiety-ridden contemporary life suggest the opposite—namely: the emotion-driven limbic system and action-oriented brain stem system shape and influence our world. Naturally, these systems support our mental health, which neuropharmacology may help us better understand and manage.

Materials and Methods

The materials used for making these works of art can be found in the Periodic Table of Elements. These creations are simply referred to here as mixed media. The creative acts of making these artworks (Figures 2-10), which include interpreting their meanings, encompass molecular and behavioral neuropharmacology. For that matter, art-making and art appreciation entail neurochemical interactions. These interactions can be understood from a neuropharmacological perspective.

For example, "Understanding Our Fears Within The Neurosphere (January 15, 1991)" (Figure 2) is an original monotype print that was created at Harel Publishers & Printers in Old Jaffa, near Tel Aviv, just three days before the first Gulf War erupted. When the artist embarked on this journey in January 12, 1991, threats of ss-1 Scud missile attacks on Tel Aviv jolted the Middle-East while raising the level of angst in adults and children alike worldwide; this angst continues to grow as our concerns for the fragile future of our world civilization grows.

The "Mind Icon" sculptures (Figures 3-6) show this jolt to our collective nervous system. Their symbolic imagery, which are 3-D pictures of mental representations, reflect the state of the world at that moment. Each sculpture presents a coronal, cross-sectional view of the human brain at the level of the thalamus, hypothalamus, hippocampus, basal ganglia and other key subcortical structures that comprise the limbic system. Their colorful abstractions of neuro-realities convey thoughts, feelings, and emotions about the nature of mind and creativity.

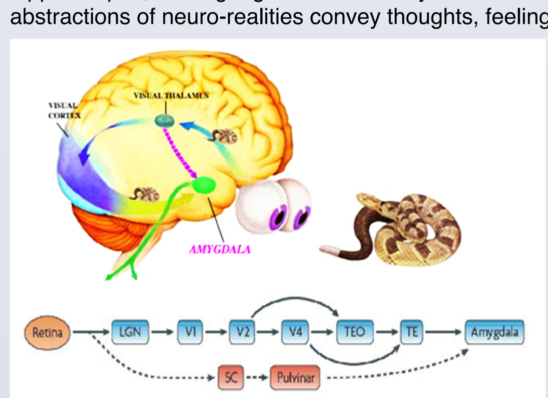

Figure 1. Illustration based on Joseph E. LeDoux, (1994) *Emotion, Memory, and the Brain*. Scientific American. Nomenclature: LGN (lateral geniculate nucleus); V1-4 (visual cortex); TEO (temporal cortex); and TE (inferior temporal cortex); SC (superior colliculus).

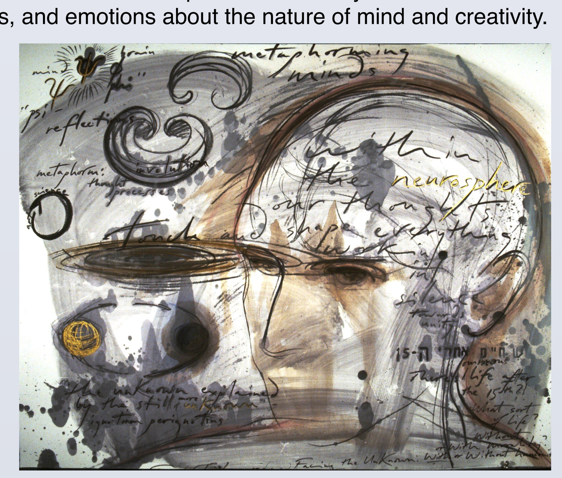

Figure 2. *Understanding Our Fears Within The Neurosphere* (January 15, 1991). Ink on paper, 28" x36". (Courtesy of Ilana Goor Museum, Old Jaffa, Israel)

In the Postscript to his article in *Psychology Today*, "The Amygdala Is NOT the Brain's Fear Center. Separating findings from conclusions", neuroscientist Joseph LeDoux wisely reminds: "there is no fear center out of which effuses the feeling of being afraid. "Fear" is, in my view, better thought of as a cognitively assembled conscious experience that is related to threat processing, but that should not be confused with the non-conscious processes that detect and control responses to threats." Having studied the neuropsychology of fear and its effects on human emotions, LeDoux cautions us to "be suspicious of any statement that says a brain area is a center responsible for some function. The notion of functions being products of brain areas or centers is left over from the days when most evidence about brain function was based on the effects of brain lesions localized to specific areas. Today, we think of functions as products of systems rather than of areas. Neurons in areas contribute because they are part of a system. The amygdala, for example, contributes to threat detection because it is part of a threat detection system" (LeDoux, 2015).

Hold these views in mind as you ponder the following speculative sculptures, paintings and art installations. Some readers may be visually attracted to these artworks because they appear to evoke fear and dare; and these individuals enjoy that emotion just as they do playing violent video games *World of Warcraft* and *Call To Duty*. Others may be instantly repelled by these images for different, subjective reasons too that have to do with their aesthetic preferences, or likes. The point is people tend to gravitate one way or another towards this art—and all works of art, for that matter. With the aid of neuroimaging tools, we can see and measure the rapid rise in neurotransmitters norepinephrine and dopamine, which modulate our emotions as reflected in our fluctuating heart rate and blood pressure. Presumably, a person wouldn't show these signs of attraction or repulsion, if they were neither attracted nor repelled by something in *the work* (i.e., concept, form, composition, problem solved, expression, etc.) *of art* (i.e., representations of thoughts, feelings, emotions, ideas, etc.). The stronger this physical sense of resonance or dissonance, the more likely the work either connects or disconnects with us. These visceral connections, or disconnections, reflect surges of dopamine or serotonin in the brain reward system (Berridge & Kringelbach, 2015) as well.

The advent of neuroimaging tools for studying the neuroscience of creativity and art (Sternberg & Lubart, 1999; Zeki, 2001; Dietrich, 2004; Kandel, 2012; Jung et al., 2013) now include wireless EEG skullcaps worn by individuals in various free range environments who are engaged in various art-making and art-appreciation activities (Contreras-Vidal et al., 2015); these tools enable researchers to generally know whether or not a person is interested or disinterested in the concept, intention, or realization manifested in the art by observing the spikes in sensory evoked potentials and comparing EEG data.

Presently, it is possible to perform reality-checks our assumptions, speculations, intuitions and insights into these brain activities using Neuroinformatics and other relational-data mining tools (Koslow & Subramaniam, 2005). These tools allow brain researchers to gain a deep knowledge of the human experience making art, as well as sharing insights into the whole process of appreciating the art. Furthermore, these technology-enabling tools help us quickly test hypotheses and suppositions, almost as quickly as mechanical engineers can rapidly prototype ideas using Computer-Aided Design tools, such as SolidWorks software. Researchers can track the intensity and frequency of our personal responses from milliseconds to minutes, in the same way neuroscientists can plot the interactions of drugs designed to inhibit or block synaptic responses within the hippocampus to two powerful stimuli: fear and anxiety (Engin et al., 2016).

One of the boldest challenges in Neuropsychopharmacology is understanding how a particular drug impacts our experiences of a particular work of art; and conversely, understanding how a specific artwork impacts the neural mechanisms that govern our experiences of art and life. Meeting this challenge will help a world of people who strive to conquer their fears and anxieties in an age that's riddled by these without relief (Stossel, 2013).

Discussion

Fear and anxiety continually rock our lives from cradle to grave. They're *perpetually nerve-wracking*, like deep cynicism, which can be countered by uplifting optimism and hope: two inexhaustible components of innovation. The "Mind Icon" sculptures (Figures 3,4, 5) appear to wrestle with our notions of human progress. On the one hand, neuropharmacologists have the know-how and means to compose maps of amino acid neurotransmitters (glutamate, γ-aminobutyric acid [GABA], glycine), monoamines and biogenic amine neurotransmitters (dopamine, noradrenaline, epinephrine, serotonin), neuropeptides, neurohormones, enzymes, receptor proteins, among other neural mechanisms that enable us to think, feel, empathize, and communicate. On the other hand, the field of neuropharmacology is still far from understanding how these neural systems work synergistically in shaping our sense of humanity. Clearly, we need more than chlorpromazine to control Combative and Explosive Behavior.

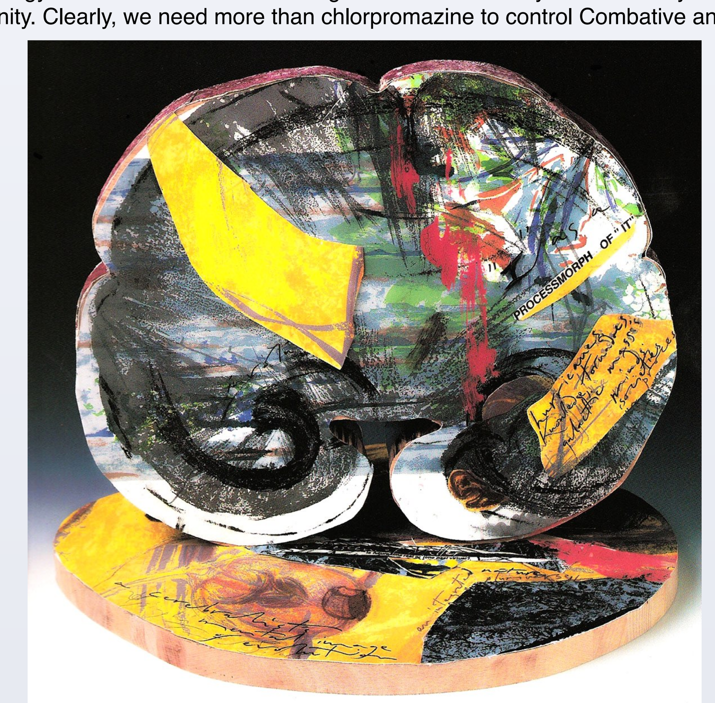

Figure 3. *Mind Icon: A Reverie of Cerebralism* (1991) mixed media on wood, 19" x 23" x 18". (Courtesy of Ronald Feldman Fine Arts, New York, NY)

These works of art address one invisible rogue 'Elephant in the room' of our world civilization, so to speak, that's charging the future of our physical well-being, as we speak. They visually maintain a sense of defiant optimism, holding out hope that sub-specialties in human neuroscience, such as neuropsychopharmacology, will advance fast enough to aid our tension-filled age of global terror "as seen on CNN" and as read in *U.S. News & World Report* (Kaplan, 2003). The artworks suggest that we can—and will—find better ways of coping with the alarming threats of global warming and environmental collapse, which many regard as today's most urgent challenge. Reputable scientific studies describe the billions of tons of anthropogenic CO2 emissions currently released into the atmosphere and forecast the trillions of tons of CH4 (methane) emissions that will be released from permafrost as the polar icecaps melt within the next 100 years. Furthermore, these artworks air our relentless fears of World World Zero fought through cyber warfare (Grossman, 2014), among other massively disruptive events. Focusing on our mental health, these symbolic sculptures ponder this common question: Why do billions of people choose to accept these ubiquitous events as part of daily life—despite how unacceptable and "unthinkable" they are? Have our nervous systems become completely habituated?

Figure 4. *Brain Icon: In-Forming A Conscionable Mind* (1991). mixed media on wood,19" x 23" x 18" (Courtesy of Ronald Feldman Fine Arts)

It's important to highlight the fact that our primary emotions—anger, sadness, disgust, and pleasure—are critical for catalyzing essential acts of innovative thinking; especially, at times when we're pressed to solve urgent problems or meet unprecedented challenges, such as the "15 Global Challenges facing humankind" earmarked by Michael Marien, editor of *Future Survey* for The Millennium Project (http://www.millennium-project.org/millennium/challenges.html). One intentional action that links all nine artworks is the lifelong quest to understand how closely human creativity relates to nature's process of creating, preserving, and destroying things (Siler, 1993).

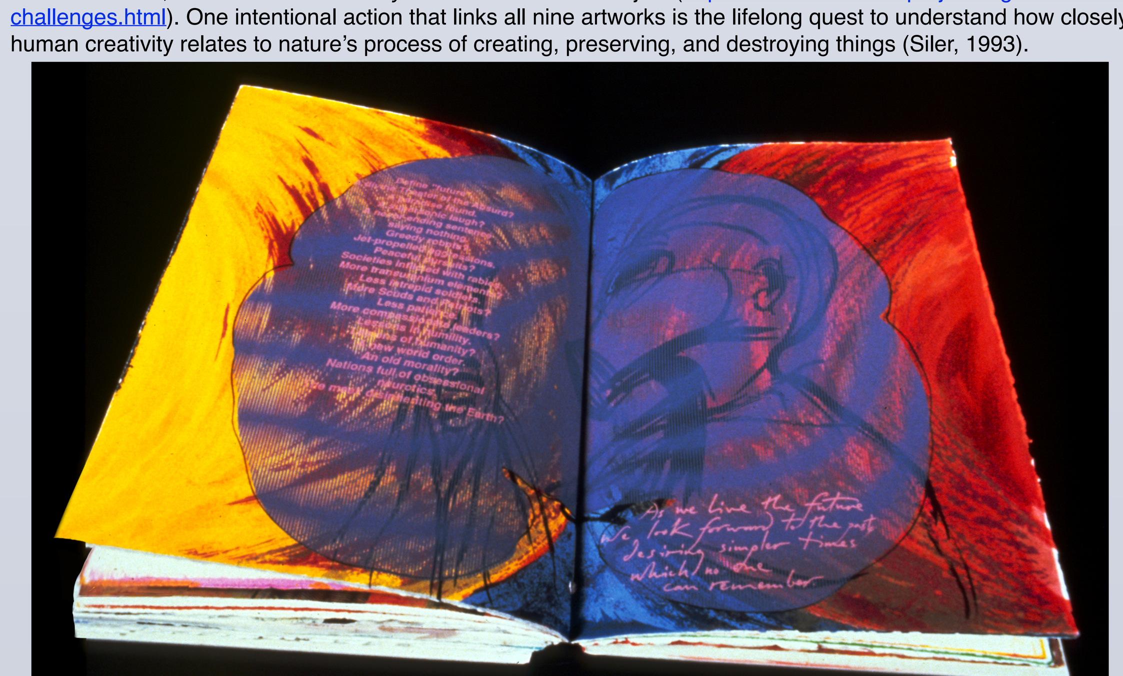

Figure 5. *Metaphorming Minds: Envisioning the Possibilities of Nature* (Old Jaffa Press, Israel, 1991). Artist's Book with 37 multi-colored serigraphs, 40 x 60cms; integrated with some of the serigraphs are 20 collaged reproductions.The handwritten note, on the right-side of this brain-shaped "Mind Icon," reads: "As we live the future we look forward to the past, desiring simpler times which no one can remember."

Results

The results from this exploratory art include purposeful, open-ended questions that grew out of ArtScience experimentations over the past four decades (Siler, 2015). How can these and other brain-based artworks be used to help further advance evidence-based research in Neuropharmacology? Although they're self-referential and speculative, they draw insights from empirical studies in the physical sciences and neurological sciences. They also explore the introspections and responses of viewers when they encounter these artworks in unique contexts, circumstances and environments.

Figure 6. *Remembering Revolutions* (1988-2011). mixed media on synthetic canvas with digital print, 24in. x 34in. x 22in. (Courtesy of Ronald Feldman Fine Arts, NYC)

Taking into account the subjectivity, introspective, and speculative nature of these artworks, neuroscientists have the means to peer into these experience-based accounts to understand why, for instance, the artist chose to layer this photomontage (see Figure 6) with a famous painting by the French Romanticist, Eugene Delacroix, titled "Liberty Leading the People" (1830). Is this artwork doing more than simply connecting past and present revolutions? Are there layers of hidden meanings that exist in this neural-like web just waiting to be discovered?

We are fast approaching a time when we can point to specific structures in the limbic system and hypothalamus, which modulate our emotions, and confidently say: Suppressing these three interconnected structures (the hippocampal formation, nucleus accumbens and amygdala) is key to coping with the anxiety and stress of fears. Nature neither makes it that clear nor easy to manipulate with neuropharmacological ingenuity. That said, recent research in human neuroscience on fear and anxiety has illuminated new functional specializations of the hippocampus, which has generally been understood as 'unitary structure'—one that processes the messy mix and mashups of cognitive and affective information relevant to learning and memory. Eigin et al. (2016) report that "different hippocampal subregions have specialized roles in other cognitive domains. Using novel cell-type- and region-specific conditional knockouts of the GABAA receptor α2 subunit, we demonstrate that inhibition of the principal neurons of the dentate gyrus and CA3 via α2-containing GABAA receptors (α2GABAARs) is required to suppress anxiety, while the inhibition of CA1 pyramidal neurons is required to suppress fear responses…our findings demonstrate a double dissociation in the regulation of anxiety versus fear by hippocampal microcircuitry."

Figure 7. *Nature's Instabilities: Gravity's Forces of Attraction Attracting Forces of Repulsion* (1986–87) mixed media on synthetic canvas with collage elements, 6ft. x 12ft. x 2in. (Courtesy of Ronald Feldman Fine Arts, NYC)

Does fear *attract* anxiety, or anxiety *attract* fear? Does boldness *repel* fear, but *attract* strong anxiety nonetheless? How do neuroscientists discern the complex mix of these two emotions *in vivo* when observing the brains of spectators experiencing "Nature's Instabilities" (Figure 7), say, in an art appreciation adventure? How does the hippocampal microcircuitry swiftly sort out these two contrasting emotions and states of mind? If viewers were informed that, in fact, this painting was expressly created to show some specific connections between mind and nature—as opposed to depicting the relationship between fear, anxiety, anger, sadness, disgust, and pleasure—would this information suddenly change our perceptions and experiences of the art? Would we feel more relaxed and calm absorbing the dynamic beauty of this art, rather than dwelling on the emotional tensions it may evoke in the uninformed? How do prescribed or recreational drugs affect our experiences?

Figure 8 consists of a series of impressionistic paintings that reconstruct a moment of inspired thought: relating the workings of the human brain to the workings of the things the brain creates (e.g., concepts, objects, innovations). The order of the constituent paintings corresponds to the patterns of the artist's own electroencephalographic (EEG) records, which run the length of the artwork and act as a timeline. Essentially, the paintings are *pictures of mental representations* of the images and objects forming in the minds' eye and imagination of the artist.

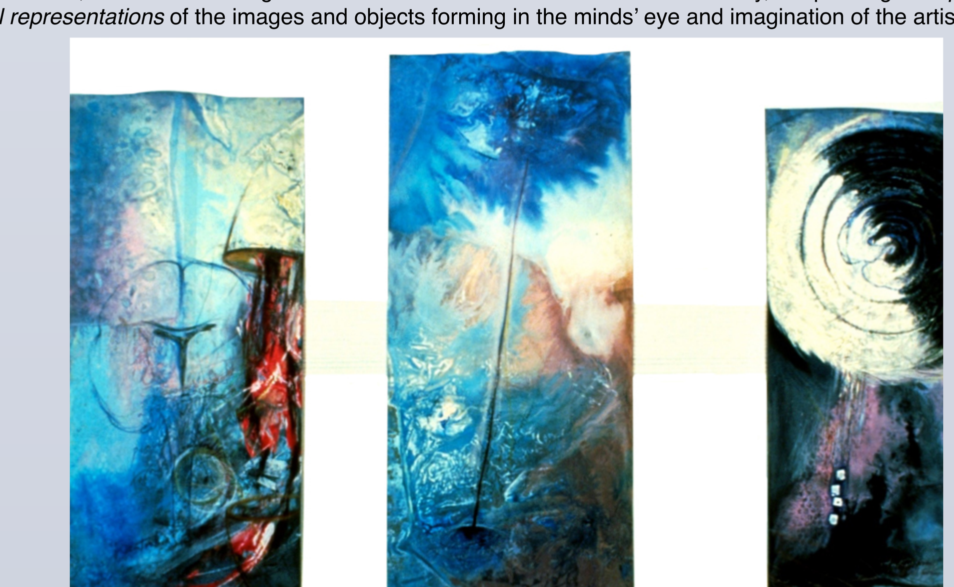

Figure 8. *States of Mind* (1985–87): (A) "In Control Out of Control", 96in. x 45"; **(B) "The Essential Connection: The Creation of Our Nuclear Minds"**, 108in. x 45in.; **(C) "Cerebral Forms"**, 91in. x 45in. mixed media on synthetic canvas with collage elements (A. Courtesy of The Solomon R. Guggenheim Museum, New York, NY; B. Courtesy of Ronald Feldman Fine Arts, NYC)

Conclusions

These metaphorical artworks (Figures 2-10) apply the *art of science* (Siler, 1990) and the *science of art* (Rakmachandran & Hirstein,1999), which combine complementary methods of creative inquiry, discovery, learning, and innovating. The resulting "ArtScience" process (Siler, 1988; Root-Bernstein et al., 2011) embraces both creative and critical thinking in the spirit of the legendary masters of the Italian Renaissance (Siler, 2012). These brain-based works of art reflect on some of the most basic questions about the nature of human creativity and its connections with nature (Siler 2012, 2015).

Figure 9. *Experiencing the Idea of Mind* mixed media on synthetic canvas, 30in. x 40in. (Collection of Suzanne Helen, Denver, CO)

Figure 9 adventures a hypothesis that the human mind is like a Klein bottle, an imaginary bottle that has no inside; rather, the inside becomes the outside. This topological concept is described as having "the mathematical property of being non-orientable," similar to a Möbius strip. It evokes many mysteries about the origin and evolution of the human mind that fill this fictitious bottle, which has no bottom to contain its infinite contents. The artist points to an area of the mind recognized as the heart of the brain: a region widely associated with the functional architecture of the limbic system, which melds our thoughts, feelings and emotions in responding to virtual, or imagined, and real experiences.

If you search the trajectory of where the sum of neuroscientific knowledge is heading and how it will be used, then these artworks may appear as signposts pointing to "the obvious": researchers will soon accurately and elegantly model the constellation of cortical and subcortical systems and their microcircuitry that make up the *connectome* (Seung, 2012). The detailed maps of the brain's neural connections are currently represented as coded "wiring diagrams". Soon, these maps will connect every neurophenomena, including our knowledge of freewill neurons (Krieman et al, 2014). But will this knowledge be used to explain away the enduring mysteries of these systems that are growing in complexity along with our understanding? This art suggests otherwise.

Figure 10 speculates on the evolutionary changes in the creative process of human beings, as neuroscientists picture them occurring over millennia (Kaas, 2009). This visionary artwork reflects on the first higher awareness humankind experienced: the moment we realized we have brains that enable us to "get a life" and not just "take a life" to survive. We could use this organ to learn from nature, rather than fear it or avoid our understanding of it.

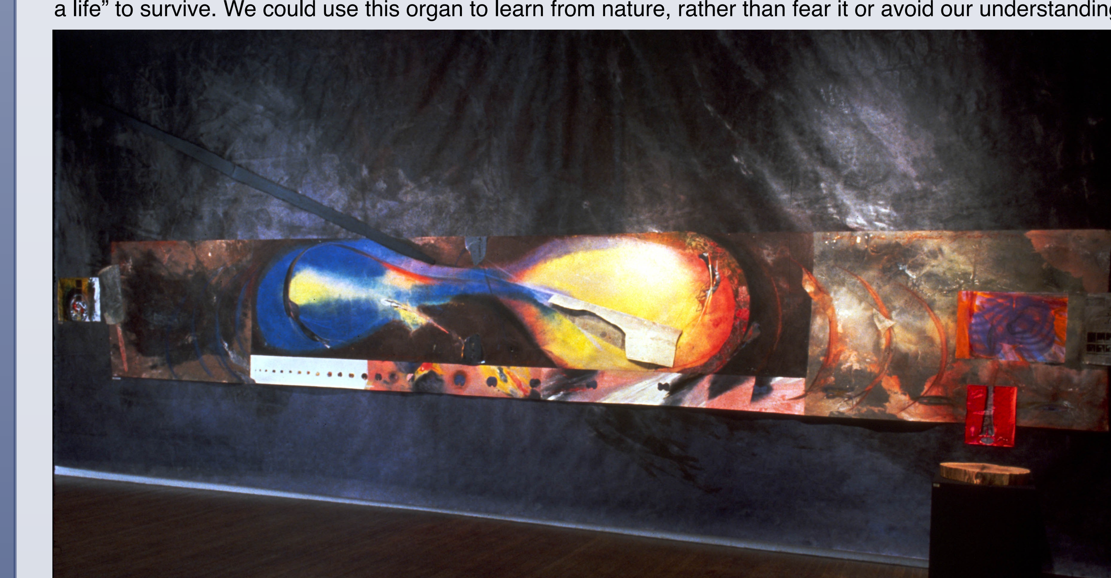

Figure 10. *The Big Bang of Consciousness* (1991-92) mixed media on synthetic canvas with collage elements, 4ft. x 24ft. x 1ft. (Courtesy of Ronald Feldman Fine Arts, New York, NY.)

This painting explores how the path of least resistance leads around violence—swerving from fear and aggression—heading towards personal freedom. "The realization that early humans were the hunted and not hunters has upended traditional ideas about what it takes for a species to thrive. For decades the reigning view had been that hunting prowess and the ability to vanquish competitors was the key to our ancestors' evolutionary success," writes Sharon Begley in her *Newsweek* article "The Evolution of Revolution" (Begley 2007). "Being hunted brought evolutionary pressure on our ancestors to cooperate and live in cohesive groups. That, more than aggression and warfare, is our evolutionary legacy."

There are countless basic questions and challenges to explore in partnership with the arts that are deeply relevant to the future of Neuropharmacology; including, questions concerning how the brain works as an Uber-pharmacy: customizing drugs to fit an individual's unique neurochemistry and neural delivery mechanisms. Imagine how the arts can help envision new ways of replicating how healthy human systems design and deliver various medicines, while devising ways of repairing damaged or diseased systems. That's an open invitation for further discoveries and innovations.

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