Juxtapositions in Trafalgar Square: tip-offs to creativity in art and science

Joseph L Goldstein

One of the delights and highlights of a trip to London is a visit to Trafalgar Square, the city's premier public space. For the past 175 years, Trafalgar Square has been England's favorite site for political rallies and national celebrations. It is also the home of the National Gallery, one of the premier art museums in the world. In the past few years, Trafalgar Square has taken on a new venture: it has become the site of a living laboratory of discovery where as many as 40,000 tourists each day can experience firsthand what creativity and innovation are all about. Before telling you about this exciting new development, let me briefly review the history and architectural layout of Trafalgar Square.

The square's name commemorates the Battle of Trafalgar in 1805, a spectacular British naval victory over France during the Napoleonic Wars. At the center of the square stands a 46-meter column on top of which sits a 5.5-meter statue of Lord Horatio Nelson, England's greatest naval hero, who was killed during the Battle of Trafalgar. Behind Nelson's Column sits the National Gallery, and surrounding the column are four large pedestals, which the British call the Four Plinths of Trafalgar. Each plinth is located at one of the four corners of the square. The first plinth carries a sculpture of King George IV on horseback. The second and third plinths are taken up by sculptures of military men whom no one has ever heard of. The fourth plinth is the most fascinating (**Fig. 1**). It consists of an imposing slab of stone that was erected in 1841 and intended to display an equestrian sculpture of King William IV. But the cost was so exorbitant that the statue was never completed, and the fourth plinth has remained bare, distorting the symmetry of the square.

Then, in 1999, a remarkable thing happened. The Royal Society of Arts came up with a bold way to solve the asymmetry problem: install on top of the fourth plinth a large contemporary sculpture that would infuse new life into 175-year-old Trafalgar Square. A commission was authorized to hold a competition every one or two years, in which about 100 artists from around the world are invited to make a proposal. The winning artist is selected on the basis of two criteria: (i) does he or she view Trafalgar Square through fresh eyes that encapsulate the collision of Trafalgar's two centuries of military heritage with the cutting edge of contemporary art, and (ii) will the artist's proposed sculpture provoke the imagination of the 40,000 tourists who visit Trafalgar Square each day?

In the past eight years, six sculptures have adorned the fourth plinth in a rolling program. I will tell you about my two favorites and the artists who produced them: Marc Quinn and Katarina Fritsch. Their work exemplifies the type of exceptional creativity that wins Lasker Awards and Nobel Prizes.

Marc Quinn's juxtaposition: female nudity and male heroism

Marc Quinn, one of the original so-called Young British Artists of the late 1980s, who is still brimming with bright ideas while approaching age 50, conceived his sculpture from an insight originating from two unconnected ideas: (i) people who go to museums gravitate to fragmented nude statuary, such as the armless *Venus de Milo*, who is admired as a great icon of feminine beauty; and (ii) people who go to Trafalgar Square view Lord Nelson, who lost one arm in battle, not as a disabled person but as a great icon of military heroism (**Fig. 2a**,**b**). Juxtaposing these two disparate insights, Quinn produced a sculpture of a nude, heavily pregnant woman who was born without arms and with shortened legs caused by a condition called phocomelia. The model for this sculpture is a critically acclaimed British artist, named Alison Lapper, who does not use artificial limbs; she paints with her mouth. Her paintings have been exhibited widely in the UK and throughout the world. In 2003, she was awarded a Membership in the Order of the British Empire (MBE) for her services to the arts.

Quinn's sculpture, entitled *Alison Lapper Pregnant*, is carved out of a single block of Carrara marble, and stands 3.6 meters high and weighs 13 tons (**Fig. 2c**). The sculpture is arresting and beautiful, yet at the same time strange and contentious—much like Velazquez's dwarfs and Picasso's eroticized biomorphic figures. The *Alison Lapper* piece stands in striking contrast to all the other monuments in Trafalgar Square, which commemorate dead, male military heroes and events of the past. The sculpture celebrates events of the future and advances a new structural model for female heroism and humanity. During the two years that *Alison Lapper* and Lord Nelson rubbed shoulders in Trafalgar Square, Quinn's sculpture—not surprisingly—elicited diverse reactions, yet during its time on display it was the most popular tourist attraction and most widely discussed event in London—a wonderful affirmation of Mark Quinn's creativity and innovation.

Katharina Fritsch's juxtaposition: British heroes and French mascots

On 20 July of this year, a giant blue bird landed on the fourth plinth and will remain there until January 2015 (**Fig. 3**). This 4.7-meter-tall rooster, provocatively entitled *Hahn/Cock*, is made of fiberglass coated with polyester resin in a deep royal blue. It was designed by one of Germany's leading artists, Katharina Fritsch, who is famous for creating oversized sculptures in a single intense color, such as yellow Madonnas, green elephants, pink apples and men in purple suits.

The creative spark that fired Fritsch's imagination may have stemmed from two unconnected ideas: (i) the rooster is an iconic symbol of male preening and posturing, and its presence in Trafalgar Square would be appropriate company for the likes of Lord Nelson, George IV and the two Victorian generals; and (ii) the

James O'Jenkins, Institute of Contemporary Art

Figure 1 The fourth plinth of Trafalgar Square. This imposing slab of stone, erected in 1841, remained bare until recently. Beginning in 1999, the City of London began a rotating program in which different contemporary sculptures are selected to adorn the bare fourth plinth; each sculpture is exhibited for a period of 1.5 to 2 years.

rooster is also the national symbol of France, serving as a mascot for sporting events such as soccer and rugby. Juxtaposing these two disparate insights, Fritsch came up with a sculptural installation that teems with humor and irony: a *French* rooster, created by a *German* artist, invades *England's* most sacred military ground that celebrates her greatest naval victory over the French. Napoleon would not be amused!

Marc Quinn's *Alison Lapper* may have rubbed shoulders with Lord Nelson, but Katharina Fritsch's *Cock* will surely ruffle the admiral's feathers. Fritsch's blue bird is destined to be the talking point among Londoners and tourists for the next 15 months, waving his tail feathers at the National Gallery and aiming his beak straight at Nelson's back.

François Jacob's juxtaposition: enzyme induction and lysogeny

Like breakthroughs in art exemplified by the likes of Quinn and Fritsch, breakthroughs in biomedical research also arise by perceiving and connecting disparate ideas. One of the most famous examples involves the work of the brilliant French geneticist François Jacob, who discovered in the early 1960s how genes are turned on and off. Jacob's insight came in a flash while watching a movie in a Paris cinema. When he closed his eyes to shut out a boring scene, he suddenly realized that two types of research going on at the Pasteur Institute that were thought to be miles apart mechanistically were in fact two aspects of the same phenomenon. Jacques Monod's work on induced synthesis of enzymes and André Lwoff's work on phage lambda and lysogeny could both be explained by a single theory involving repressors that inhibit gene activity.

François Jacob died earlier this year at age 92. The key to his creativity, as pointed out in multiple obituaries, was his masterful ability to see juxtapositions and analogies where others saw only separate phenomena.

Arthur Koestler's theory of creativity

The concept that new ideas arise by the generation and juxtaposition of random combinations was first authoritatively examined by the Hungarian-British writer Arthur Koestler in his classic 1964 book, entitled *The Act of Creation: A Study in the Conscious and Unconscious Processes in Humor, Scientific Discovery, and Art*. According to Koestler, the creative activities of scientists and artists are closely related to those of comedians. The hallmark of a good comedian is one who thinks the unthinkable—not by thinking outside the box but by mentally uniting several boxes of unconnected thoughts to create a totally novel thought, which becomes the punchline of a good joke.

Koestler chose to illustrate his point by analyzing a joke popularized by Sigmund Freud in his essay on wit and paraphrased below:

> The marquis finds his wife in bed with a bishop. He doesn't say a word, but goes to the window and blesses the people walking under it. When his wife asks him what he thinks he is doing, he replies, "He is performing my function; I will perform his."

This joke juxtaposes two normally dissimilar contexts, marital honor and the division of labor. This unexpected union produces an intellectual innovation—a eureka moment, which is the essence of any creative action, whether it be a good joke, a scientific discovery like Jacob's repressor theory, or a memorable piece of art like Quinn's *Alison Lapper* or Fritsch's *Cock*.

In the past 50 years, thousands of books and articles have been written on the subject of inno-

Figure 2 Marc Quinn's sculpture for the fourth plinth, and the juxtaposition that inspired it. (**a**) Alexandros of Antioch (Hellenistic Age), *Venus de Milo*. ~100 BC. Marble. Height, 2.0 meters. Louvre Museum, Paris. (**b**) Edward Hodges Baily, *Horatio Nelson*. 1843. Sandstone. Height, 5.5 meters. Trafalgar Square, London. Both arms of the *Venus de Milo* were lost following discovery of the fragmented sculpture in 1820 on the island of Milos. The right arm of Lord Nelson was lost in battle. (**c**) Marc Quinn, *Alison Lapper Pregnant*. 2005. Height, 3.6 meters. Exhibited on the fourth plinth at Trafalgar Square, London, 2005–2007 (**a**,**c** from R. Rogers, M. Quinn and M. Mack, *Fourth Plinth*, Steidl, 2008).

vation and creativity, virtually all of which deal directly or indirectly with Koestler's original ideas. Two well-known examples of his influence are echoed in Jacob Bronowski's famous quote "The creative mind is a mind that looks for unexpected likenesses" and in Steve Jobs's dictum "Creativity is just connecting the dots."

Even though we have a general idea of how the juxtaposition of disparate ideas produces creative art and creative science, how the brain generates these juxtapositions at the biological and psychological levels is a great mystery waiting to be solved—the Grand Challenge of Creativity.

The last word on any discussion on creativity belongs to arguably the two most creative individuals of the past 100 years, Albert Einstein and Pablo Picasso. Both were asked by journalists, "What is creativity?" Einstein's response: "The secret to creativity is knowing how to hide your sources." Picasso's response: "I don't know, and if I did I wouldn't tell you."

Basic Award: discovering how neurotransmitters are released

This year's Lasker Basic Medical Research Award is given to two scientists for their discoveries concerning the molecular machinery and regulatory mechanisms that underlie the rapid release of neurotransmitters. The two recipients are Richard H. Scheller (Genentech) and Thomas C. Südhof (Stanford University), who 25 years ago independently embarked on a bold initiative to delineate the molecular basis of synaptic vesicle fusion and its regulation by calcium.

Neurons communicate with each other by releasing chemical neurotransmitters into synaptic clefts that separate presynaptic and postsynaptic cells. The synaptic release of neurotransmitters is the basis of all neural function—from sensory perception to movement, from reasoning to memory. Hitting a baseball traveling more than 90 miles an hour is one of the most complex tasks imaginable, requiring the player to receive sensory information (see the ball), interpret it (process its image in the visual cortex) and respond (decide whether to swing) in about 200 milliseconds—all of which result from the coordinated transfer of neurotransmitters across billions of synaptic clefts between presynaptic and postsynaptic neurons.

Neurotransmitters are packaged in tiny synaptic vesicles, each containing ~5,000 transmitter molecules that are released from the presynaptic neuron when an electrical action potential arrives at its nerve terminal and opens voltage-gated calcium channels. Calcium floods into the terminals, where it triggers the fusion of pre-docked synaptic vesicles with the plasma membrane and opens the fusion pore, allowing the all-or-none (or quantal) release of neurotransmitters.

The key role of calcium in triggering rapid and quantal release was first described 50 years ago by Bernard Katz, for which he received the Nobel Prize in Physiology or Medicine in 1970. The molecular machinery responsible for the calcium-triggered release of neurotransmitters was a complete mystery that began to be solved in the late 1980s when Scheller and Südhof initiated their now-classic studies. Both of them started their research on synaptic vesicles as newly appointed assistant professors—Scheller at Stanford University and Südhof at the University of Texas Southwestern Medical Center in Dallas.

At the time Südhof and Scheller began, not a single protein important for neurotransmitter release had been functionally characterized. Genetic screens by the laboratories of Sydney Brenner and Randy Schekman had identified gene mutations that disrupted synaptic transmission in *Caenorhabditis elegans* or blocked processing of proteins in the secretory system in yeast, but the nature of the corresponding genes and the function of the encoded proteins were not known.

After several decades of intense and original research involving an impressive array of approaches (biochemical, biophysical, cell biological, electrophysiological and targeted mouse genetics), Scheller, Südhof and their colleagues had molecularly identified and functionally characterized the major proteins involved in neurotransmitter release, and they had also worked out the fundamental mechanism of its regulation by calcium. Although Scheller focused primarily on the assembly of the fusion machine and Südhof primarily on the calcium-triggered regulatory mechanism, both of them contributed synergistically to the neurotransmitter secretion story. From their original work and that of others, the following model (briefly summarized here) has emerged:

Synaptic vesicle fusion is mediated by a molecular complex formed by three membrane proteins: one protein (VAMP/synaptobrevin) residing on the synaptic vesicle and two proteins (SNAP-25 and syntaxin) on the target plasma membrane. VAMP/synaptobrevin is referred to as a v-SNARE (v for vesicle), and SNAP-25 and syntaxin as t-SNARES (t for target). These v- and t-SNAREs assemble to form a ternary complex that directs the two membranes toward each other, creating membrane curvature and tension and producing an intermediate state of hemi-fusion. Munc18-1, a soluble protein, also appears to be essential for synaptic vesicle fusion by complementing SNARE complex assembly in fusion.

Opening of the fusion pore and release of a bolus of neurotransmitters is triggered by the influx of calcium. This action of calcium is mediated by its binding to synaptotagmin, a synaptic vesicle membrane protein that functions as the main calcium sensor in the system. Calcium binding to the two C2 domains of synaptotagmin induces the association of synaptotagmin with the phospholipids of the hemi-fused membranes, which in turn opens the fusion pore to trigger release. Synaptotagmin cooperates with a SNARE-associated soluble protein called complexin. In the absence of calcium, complexin acts as

Andy Rain, *The Telegraph*

Figure 3 Katharina Fritsch, *Hahn/Cock*. 2013. Fiberglass coated with polyester resin. Height, 4.7 meters. Exhibited on the fourth plinth at Trafalgar Square, London, 2013–2015.

a clamp to arrest the fusion reaction; when calcium is present, synaptotagmin releases the complexin block, thus ensuring tight and rapid regulation of fusion-pore opening and release of neurotransmitters. After transmitter release, the SNARE complex is disassembled by an ATPase called NSF, an action essential for multiple rounds of fusion and release.

In 2002, James Rothman and Randy Schekman received the Lasker Basic Medical Research Award for their discoveries of the mechanism that orchestrates the budding and fusion of membrane vesicles in non-neuronal cells. One of the proteins that Rothman and Schekman found to be required in their *in vitro* fusion reactions in mammalian and yeast cell extracts was NSF (SEC18 in yeast). In the course of identifying new proteins that interact with NSF, Rothman discovered in 1993 that bovine brain (a fortuitous choice of tissues, in retrospect) contained three membrane proteins that formed a complex that bound tightly to his NSF affinity column. The three proteins—which he named SNAREs—turned out to be identical to three of the synaptic vesicle proteins—VAMP/synaptobrevin, syntaxin and SNAP25—that Scheller, Südhof and others had identified earlier. Rothman's affinity column experiment immediately implicated these three proteins in synaptic vesicle fusion, a finding that rapidly catalyzed research in the fast-moving field of neurotransmitter release.

In addition to Rothman's contribution, the work of Scheller and Südhof was advanced by contributions from many other scientists: Cesare Montecucco (University of Padua), who first reported in 1993 that SNARE proteins are the substrates for tetanus and botulinum neurotoxins that selectively block synaptic vesicle fusion via proteolytic cleavage; Reinhard Jahn (Max Planck Institute for Biophysical Chemistry, Göttingen) and Axel T. Brunger (Stanford University), who together provided structural evidence for the tight assembly of the SNARE fusion complex; and Reinhard Jahn (Göttingen) and Josep Rizo (University of Texas Southwestern Medical Center, Dallas), whose long-time collaboration with Südhof led to the biophysical and genetic discovery that synaptotagmin is the long-sought calcium sensor.

One of the great philosophers of science, Karl Popper, wrote an essay in 1965 entitled "Of Clouds and Clocks," in which he divided scientific phenomena into two categories: those with a known mechanism ('clocks') and those with unpredictable behavior ('clouds'). The current understanding of synaptic vesicle fusion and function at a detailed biochemical level explains the mechanism of a fundamental biological problem, which in the Popper sense has moved the problem from 'cloud' to 'clock'.

Inspired by Popper's essay, the contemporary American artist Terry Winters, known for his lush abstract paintings influenced by biological structures, recently created a series of prints and paintings entitled *Clouds and Clocks*. One of Winter's paintings resembles a synaptic vesicle filled with neurotransmitters (**Fig. 4**). Even though Scheller's and Südhof's work has moved us into the 'clocks' of regulated neurotransmitter release, we remain in the 'clouds' in terms of understanding how alterations in synaptic vesicle proteins influence diseases of the brain and abnormalities in behavior. Hopefully, this cloudy situation will clear up as the US National Institutes of Health's newly inaugurated Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative teaches us more and more about how the brain works.

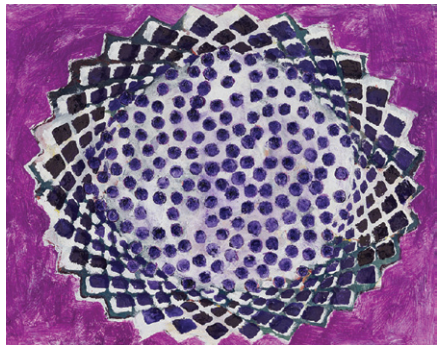

Figure 4 Terry Winters, *Clocks and Clouds/5.* 2012. Oil on linen. 65.4 × 84.5 centimeters. Courtesy of Matthew Marks Gallery, New York City.

Clinical Award: creating a prosthetic sensory organ

This year's Lasker~DeBakey Clinical Medical Research Award is given to Graeme M. Clark (University of Melbourne), Ingeborg J. Hochmair (Med-El, Innsbruck) and Blake S. Wilson (Duke University) for the development of the modern cochlear implant, a device that bestows hearing on individuals with profound deafness. More than 320,000 people have received cochlear implants, either in one or in both ears.

Impairment in hearing affects as many as 600 million people worldwide, most of whom can be helped with hearing aids that amplify sound. But about 10% of deaf people with severe sensorineural hearing loss cannot hear at all, owing to genetic disorders, infections (rubella and meningitis), certain drugs (kanamycin, streptomycin and cisplatin) or overexposure to loud sounds. In such deaf people, hearing aids are of no benefit because sound cannot be transmitted to their brain, no matter how much it is amplified. This is because the sensory hair cells of the cochlea, a snail-shaped structure in the inner ear, are severely damaged.

In people with normal hearing, sound travels through the external ear canal to the eardrum, which transfers the vibrations in the air to three tiny bones in the middle ear. The innermost of these bones relays the vibrations to the cochlea's basilar membrane, where the delicate sensory hair cells are arranged in a precise way. The ~20,000 hair cells in each cochlea respond to the incoming vibrations and convert them into an electrical signal that travels along 30,000 auditory nerve fibers. The nerve fibers in turn transmit the acoustic information along the eighth cranial nerve to the brain, where the original sound is interpreted. The cochlea is organized tonotopically, such that hair cells located at different sites along the basilar membrane are stimulated by different sound frequencies in a highly organized fashion that is projected in an identical pattern through the auditory nerve fibers to the brain.

As recently as 35 years ago, there were no effective treatments for profound hearing loss resulting from severely damaged hair cells. Such treatments were considered impossible because of the engineering challenge of bypassing a defective cochlea so as to stimulate the auditory nerve fibers in a tonotopic way that would faithfully reflect different sound frequencies. A key historical event in cochlear implant research occurred in 1961, when William F. House, a physician and otologist in Los Angeles, inserted a gold wire a short distance into the cochlea of two of his deaf patients. Electrical stimulation of this single electrode allowed the patients to hear sounds, but they could not understand speech. This initial surgically implanted device was eventually rejected by the body. But after many years of refining the materials of his implants, House produced a long-lasting version that was successfully implanted in 1969. With this improved device and subsequent ones that he and others developed, limited speech perception was achieved in a few patients.

Despite notable improvements in the House single-channel device, most otologists as recently as the late 1980s questioned the theoretical rationale of House's approach. How is it possible that stimulating the cochlea with only a single implanted electrode can substitute for the 20,000 sensory hair cells and 30,000 auditory nerve fibers normally required to produce acoustic information in the brain? Despite the controversial nature of his work, House (who

died last year at age 89) was clearly a pioneer whose one-channel device paved the way for the therapeutically effective multichannel devices developed during the past 20 years by this year's Lasker~DeBakey winners.

Graeme Clark and Ingeborg Hochmair are largely responsible for the key hardware developments and Blake Wilson for the key software strategies that made possible the modern prosthetic cochlear device: the so-called multichannel implant. A typical multichannel implant consists of several components: a small microphone for picking up the sound (worn behind the external ear), a highly miniaturized digital speech processor for converting the sound into electrical signals, an external and internal transmission system for relaying the signal to the implanted components, and a tiny array of 12–22 electrodes that is surgically implanted into the cochlea for delivering the electrical signals to the auditory fibers of the cranial nerve.

In the multichannel devices designed independently by Hochmair and Clark, the implanted electrode array takes advantage of the tonotopic representation of stimulus frequency along the basilar membrane of the cochlea. Each individual electrode in the prosthesis is designed to excite a single subset of auditory nerve fibers that are sensitive to similar sound frequencies, and the combined set of 12–22 electrodes in the array stimulates 20–24 different subsets of auditory fibers, thus mimicking a complex sound composed of many different frequencies. In addition to their innovative design developments, Hochmair (together with her husband Erwin S. Hochmair) and Clark directed or spun off two of the three main companies that brought cochlear implants to the marketplace.

In pioneering the software aspects of the modern cochlear implant, Blake Wilson and his colleagues solved the tricky problem of turning acoustic signals into multichannel electrical stimuli; that is, delivering electricity to an electrode array with 12–22 electrodes in a manner that would reflect the tonotopic actions of the cochlea's 20,000 hair cells and the 30,000 auditory nerve fibers. Wilson's speech strategy, referred to as continuous interleaved sampling (CIS), filters speech or other input sounds into bands of different frequencies. The output of each band is then channeled into a single electrode of the implanted array, thus mimicking the general frequency mapping of the normal cochlea.

Figure 5 Robert Gober, *Untitled.* 2008. Cast gypsum polymer. 36 × 27 × 15 centimeters. Courtesy of Matthew Marks Gallery, New York City.

Helen Keller wrote, in a letter to J.K. Love, MD (which accompanied a paper by him in *Laryngoscope* **20**, 596–611, 1910):

> I am just as deaf as I am blind. The problems of deafness are deeper and more complex... than those of blindness. Deafness is a much worse misfortune. For it means the loss of the most vital stimulus—the sound of the voice that brings language, sets thoughts astir, and keeps us in the intellectual company of man.

Thanks to the accomplishments of Clark, Hochmair and Wilson, as well as the contributions of numerous other electrical engineers and otologists, most users of modern cochlear implants can now communicate with ease in everyday conversation and are no longer deprived of "the intellectual company of man." To cite one example, most implant users have no difficulty with cell phone conversations. The use of the cochlear implant device by a previously deaf person is unquestionably a life-changing event.

The American contemporary artist Robert Gober, known for his three-dimensional sculptures of everyday objects and isolated body parts, has created an isolated human ear cast in a gypsum polymer (**Fig. 5**). The ear hangs alone on the wall, listening and eavesdropping on the viewer, who wonders whether the person who was the model for this ear has normal hearing or whether he or she is totally deaf and can have his or her hearing restored with a cochlear implant.

Joseph L. Goldstein is Chair of the Lasker Awards Jury.
e-mail: *joe.goldstein@utsouthwestern.edu*

Lasker Award recipients receive an honorarium, a citation highlighting their achievement and an inscribed statuette of the Winged Victory of Samothrace, which is the Lasker Foundation's symbol of humankind's victory over disability, disease and death.

To read the formal remarks of speakers at the Lasker ceremony, as well as detailed information on this year's awardees, please refer to the Lasker website at http://www.laskerfoundation.org/.

COMPETING FINANCIAL INTERESTS
The author declares no competing financial interests.