Memory, Mind, and Neuroscience

by

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Recently, I watched a 'TED' talk (TED is an acronym for 'Technology, Entertainment, and Design'). The talk was given by two neuroscientists, Steve Ramirez and Xu Liu, and took place in Boston, June 2013.

The presentation was based on research that led to several publications that appeared in the science journals, *Nature* and *Science*. The title of the *Nature* article is: 'Optogenetic stimulation of a hippocampal engram activates fear memory recall' and was published in early 2012, while the *Science* report was entitled: 'Creating a False Memory in the Hippocampus' and was published in July 2013.

All of the foregoing will be elaborated upon shortly. However, first, I would like to create a context for the critical reflection that will give expression to my comments concerning the research of the two aforementioned neuroscientists.

Toward the end of the June 2013 TED presentation, Steve Ramirez indicated that one of the purposes of their talk was to bring people up to date on the kinds of research that were taking place in neuroscience, as well as to acknowledge (even if only vaguely) the existence of various ethical issues raised by their research, and, finally, to invite people to join in the discussion with respect to their research. Steve's co-presenter, Xu Liu, also stipulated at one point near the end of the talk that their research was rooted in a philosophical principle of neuron science – namely, that, ultimately, mind is a function of physical stuff … stuff that can be "tinkered with" and a tinkering process that is limited only by our imagination.

On the one hand, the following comments constitute my acceptance of the aforementioned invitation from Steve Ramirez during the June 2013 presentation for people to join in the conversation concerning their research. Consequently, part of my comments will address some of the ethical concerns that were alluded to by Steve Ramirez during the Boston presentation, while another aspect of my comments – perhaps the more central dimension of such comments -- will revolve around an exploration of the philosophical principle cited by Xu Liu that is at the heart of neuroscience and which, as indicated earlier, seeks to reduce mental phenomena to biological, material, or physical events.

Let's begin by providing an outline of the experimental model employed by Steve Ramirez and Xu Liu. Among other things, that model involves introducing mice to a few methodological bells and whistles.

Optogenetics (a word which appeared in the title of the aforementioned *Nature* article) is a term that – as the sub-components of the word might suggest – involves combining optical and genetic properties in certain ways. Essentially, microbial or viral genes are engineered to become receptive or sensitive, in some manner, to light or optical energies and, thereby, such genetic residues are enabled to, in effect, serve as a target for light sources (e.g., lasers) that will induce the target molecules to serve like switches that are capable of turning certain aspects of cellular functioning on and off when the genetically engineered concoction is injected into, say, mice and, subsequently, activated by laser stimulation.

In their presentation, Ramirez and Liu also point out that there is a biological marker or indicator present in cells that signifies certain kinds of activity have taken place in those cells. Therefore, part of the process of genetic engineering employed in the optogenetics technique is to take a molecular component that has a sensor-like capacity that is able to detect the presence of the aforementioned cellular indicator or marker signifying recent cellular activity and, then, splice that sensor component to the aforementioned molecular/genetic switch that, subsequently, can be activated and deactivated through the application of targeted laser energies.

In the case of the Ramirez-Liu experiments, the 'switch' portion of the genetically engineered component is channelrhodopsin. This is a membrane protein that controls the flow of certain ions (for example, sodium – Na+) into the interior of a cell. Modifying the flow of ions into a cell is possible because channelrhodopsin is a protein whose three-dimensional conformation can be altered when stimulated by, among other things, laser light and, in the process, open or close the membrane channel-way with respect to ion flow, thereby affecting the functioning of such a cell.

To sum up, the general idea employed by Ramirez and Liu in their experiments is to identify cells that are involved in, for example, memory formation through the manner in which those cells will leave an activity signature or marker. This marker can be detected by the genetically engineered sensor-switch component and, this, in turn, will transform the cell into a target that is believed to have something to do with memory formation and which -- when deemed appropriate by the researchers – can be activated by stimulating the switch side (i.e., the membrane protein channelrhodopsin) of the generically engineered virus with laser light.

For quite some time, the hippocampus (a ridge section found along the bottom of the lateral ventricle portion of the brain – there are two such ridge sections) has been implicated (via an array of experimental and clinical evidence) as playing an important role of some kind with respect to memory formation. Thus, when one scans the title of the aforementioned *Nature* journal article – i.e., 'Optogenetic stimulation of a hippocampal engram activates fear memory recall' – and understands that the term "engram" is a way of referring to a memory trace that has arisen through a hypothesized change (temporary or permanent) in brain chemistry within the hippocampus, then one is being told by the *Nature* article title that the Ramirez/Liu experiment is one which uses optogenetic methods (outlined previously) to bring about the activation (or recall) of memories involving fear.

In 2000, Eric Kandel received the Nobel Prize for research that helped establish the nature of some of the physiological dynamics that are associated or correlated with memory formation/storage in Aplysia -- a sea slug whose relatively large nerve cells made it a good candidate for trying to scientifically analyze what happens biochemically when learning or memory formation occurs in those life forms. To make a much longer story somewhat shorter, Kandel and other researchers discovered -- while studying the gill-withdrawal reflex in Aplysia -- that sensitization and habituation (which are both forms of learning and, therefore, constitute instances of memory formation) were associated with the release of

certain kinds of molecules -- [e.g., c-Amp – the so-called second messenger of the cell, serotonin (a neurotransmitter), PKA (c-AMP dependent kinase), and CREB (c-AMP response element binding protein) -- that appeared to play important roles in short-term and long-term memory formation, as well as were implicated in the processes that converted short-term memory into long-term memory.

The generation of the foregoing sort of cascade of biochemical molecules also was correlated with increases in synaptic complexity or connectivity. As a result, Kandel came to believe that changes in synaptic connectivity were indications that learning/memory was somehow being established through those synaptic enhancements, and, in turn, those changes in synaptic connectivity were some kind of a function – although many of the details were lacking with respect to the precise dynamics of that function -- of the cascade of biochemical changes that were taking place within neurons.

Mice are more complex than Aplysia, and humans are more complex than either mice or Aplysia. Nonetheless, ever since the work of Kandel began back in the 1960s, a great deal more biochemical, physiological, cellular, and neuronal evidence has been generated that is consistent with the idea that when certain (a) biochemical changes in cellular physiology are correlated with (b) changes in synaptic connectivity that are correlated with (c) differences in behavioral activity over time, and when the foregoing three elements occurred in relatively close temporal (if not spatial) juxtaposition to one another, then the collective presence of those three elements was interpreted to indicate that learning or memory had been generated … and, this remains the basic idea concerning the issue of memory formation irrespective of whether one is talking about Aplysia, mice, humans, or any other life form that is capable of exhibiting a capacity to learn or retain memories (short-term or long-term) with respect to on-going experience.

Naturally, the physical/material details of learning and memory might change as one moves from species to species. Nevertheless, a growing body of evidence lends support to the idea that learning/memory are entirely functions of physical/material events.

The Ramirez/Liu research that was outlined in the June 2013 TED talk is a continuation of the foregoing perspective. The two investigators took mice and surgically implanted a means of delivering laser stimulation to the hippocampus portion of a mouse's brain that also had been equipped with a genetically engineered 'sensor-switch' which could detect recent activity in cells that seemed to be involved in the formation of memories concerning fear in the experimental animals.

More specifically, the researchers placed a number of surgically altered, and genetically engineered mice into a chamber where an electrical shock was applied to the feet of the animals. As a result of this experience, certain cells in the hippocampus portions of the mice brains became active, and this activity left a biochemical footprint that was detected by the genetically engineered sensor-switch

which had been injected into the mice through a viral host and, as a result, served as target candidates for subsequent laser stimulation.

The fact specific cells became active during the shocking process was interpreted by the researchers to signify that a memory had been formed. However, a number of questions can be raised concerning that kind of interpretation.

To begin with, what does it mean to say that a cell has left a marker indicating that the cell has been active recent? Active doing what?

The presumption of Ramirez and Liu is that the cellular activity gives expression to processes that are involved in learning or memory formation. However, one could ask in relation to such activity: Involved how?

How does a neuronal cell's activity generate learning or memory formation? Where, exactly, is the memory amidst such cell activity?

Is learning/memory in the cells that have been activated? If so, what is the form of the dynamic structure or process that is said to 'hold' the memory in the cells – whether considered either individually or collectively? Or, is the memory of fear to be found in the synaptic changes that follow from the changes in cell chemistry. Or, is it some combination of the foregoing two possibilities.

According to Ramirez and Liu, the process works as follows. First, the three-dimensional conformation of channelrhodopsin is induced to change. As a result, certain ions begin flowing into the interior of the cell.

In turn, the ion influx leads to a cascade of metabolic processes involving, among other things, c-AMP, serotonin, CREB, PKA, and other bio-molecules. Where is the memory or learning in all of this, and how did this cascade of cellular denizens come to signify or be interpreted to mean "fear"?

Kandel and others believed that the foregoing cascade of events was functionally related to changes in synaptic connectivity and that it was this transformation in synaptic connectivity and complexity which signified that learning had occurred or a memory had been formed. So, does the memory reside in the synaptic connections, and, if so, how is the memory instantiated in those connections, and if the memory is held through those synaptic connections, what determines the holding pattern and what 'reads' that pattern to understand that it is a memory which holds one kind of learning rather another?

What is the relationship between, on the one hand, cells (the sort of cells in which Ramirez and Liu are interested and for which they have genetically engineered their sensor-switch mechanism) that are active during memory formation and, on the other hand, changing synaptic connectivity (which people such as Kandel believed was central to learning and memory formation)? If memory is in the cells – as Ramirez and Liu seem to believe – then what is the significance of the changes in

synaptic connectivity and how does what transpires in the cell shape, color, and orient those synaptic changes?

Alternatively, one might ask what determines which cells will be initially activated to become part of the fear learning or fear memory process? Or, what determines which biochemical, electrical, and physiological changes will take place within cells that will permit an organism to differentiate learning/memory experiences over time. After all, if the same cellular components (e.g., c-AMP, serotonin, PKA, CREB, etc.) are thought to be at the heart of memory formation, then how are those components put together in distinct packages that would enable an organism to differentiate among memories? Or, what determines the pattern of synaptic connectivity that will take place and which can be said to hold – allegedly – this or that form of memory/learning, and what is it about the structural or dynamical character of enhanced synaptic connectivity that gives expression to memory?

One might also critically reflect on the nature of the differences between the original existential circumstances that led to the – alleged – formation of a fear memory, and the quality of that memory relative to the actual event. People who suffer from PTSD have vivid, intense, flashbacks, and, consequently, there seems to be a dimension of intensity associated with such flashback memories that is comparable to the original circumstances out of which the memories arose.

However, memories are not always as vivid and intense as the original circumstances from which they were derived or on which they are based. So, the fact that a given memory in a mouse is activated doesn't necessarily explain – in and of itself – why such a memory should necessarily lead to the response of freezing, and, therefore, one is left with the possibility that something might be going on in the experiment other than what Ramirez and Liu are hypothesizing to be the case.

Mice appear to have some degree of awareness or consciousness. How do cellular and synaptic changes generate phenomenology or how does phenomenal experience arise out of those changes?

When a mouse receives a shock to its feet, does the mouse experience fear or does it experience pain? Or, is the mouse experiencing stress?

There is a behavioral response in mice known as "freezing". This consists in a set of behavioral dispositions in which the mouse remains very still and, possibly, vigilant when immersed in a given existential situation that is considered threatening in some way.

Once a mouse has been shocked and, then, subsequently, exhibits, freezing, this doesn't necessarily mean that the mouse is experiencing fear or remembering fear while in the condition of freezing (although this might be the case). Instead, the mouse might be exhibiting a form of coping strategy (which could be instinctual rather than learned) that is intended to either help avoid subsequent shocks or deal with the pain of having been shocked, and if so, perhaps the primary phenomenological component under such circumstances is merely heightened

vigilance with an inclination in the mouse toward escaping or avoidance when possible.

Alternatively, freezing in mice might represent a state of shock. Possibly, a mouse that is exhibiting freezing behavior might not either be in pain or in a state of fear, but, rather, is just stunned and directionless with respect to how to proceed or what to do next … somewhat like a prize fighter who has been rocked by a punch and is merely trying to stay on his or her feet but with very little focused awareness with respect to just what is going on around him or her.

A variation on the foregoing possibility is that 'freezing' in mice might be a response to stress rather than an expression of fear. Pulled in different direction by various internal and external forces, a mouse might freeze up, and, consequently, the associated phenomenological state is one of stress rather than fear.

The fact of the matter is that we don't know what is going on in the phenomenology of a mouse during the state of freezing. Is the mouse afraid, in pain, in shock, stressed, uncertain, vigilant, wanting to get away, remembering a previous, similar problematic experience, or is the mouse experiencing some combination of all of the foregoing possibilities? We don't know.

Freezing is a behavioral disposition that is exhibited by mice during certain circumstances. Freezing in mice is a coping strategy and/or an instinctual behavioral response.

Learning or memory formation might play some sort of modulating role with respect to how that behavioral response manifests itself within different circumstances. Nevertheless, we don't necessarily understand what is triggering the behavioral response of freezing or what the precise properties and dynamics of the triggering event are.

Is the freezing response being triggered by a memory? If so, how does the memory lead to the initiation of the behavior?

Moreover, mice have a more expansive repertoire of behavior than just freezing. Sometimes they fight and sometimes they take flight?

What if the freezing is an indication that the mouse is uncertain about whether to pursue fighting or fleeing? What if the freezing indicates indecision rather than fear, stress, pain, or shock?

Perhaps, freezing means different things to a mouse in different circumstances. On some occasions, it might be an expression of fear, but on other occasions it might indicate stress, indecision, or a vigilant wait for the sort of information that might push the mouse toward fighting or fleeing.

We don't know what, if any, phenomenology is associated with that behavioral response. We don't know what, if anything, the cellular and synaptic changes that

have been described by neuroscientists since the time of Kandel have to do with the generation of that phenomenology.

There is no neuroscientist on the face of the Earth who has yet been able to demonstrate how one goes from cellular changes in neurons to enhanced synaptic connectivity, and, then, is capable of proceeding on to demonstrate how the phenomenology of memories of a particular character and quality arise from those cellular and synaptic changes. All scientists have established so far is that there is a correlation between certain kinds of biological events and the appearance of the sorts of behavior that seem to suggest that learning has taken place or a memory has been formed, but, unfortunately, some scientists have jumped to unwarranted conclusions concerning the connection between biological activity and the phenomenology of experience.

Consider the following idea. One can probe the electronic intricacies of a television set all one likes – even down to the quantum level. However, such analysis will do nothing to tell one where the content and structure of the picture comes from that is made manifest through the television set.

As is the case with television sets, so too, biology, cell physiology, and synaptic connectivity might play a necessary supporting role with respect to the phenomenology of experience. Nonetheless, biology alone might not be sufficient to account for the character of the content that is given expression through the phenomenology of experience.

A television set plays a necessary supporting role with respect to being able to generate a picture on its screen but that same electronic device cannot account for why the picture has the content, structure, and quality it does. To account for the latter phenomenon, one needs to talk about television stations, writers, authors, directors, actors, producers, and viewers … all of which exist beyond the horizons of the television set, just as a proper explanation for memory or learning might exist beyond the horizons of purely biological considerations – at least as those considerations are currently understood.

Let us return to the Ramirez/Liu experiment. Under normal circumstances, when a mouse is placed in an experimental box, the animal exhibits exploratory behavior … sniffing and scurrying its way around the interior of the apparatus.

If the feet of the mouse are shocked during the exploratory process, the mouse, subsequently, might begin to display freezing behavior. According to Ramirez and Liu, the mouse has formed a memory of fear, and this state of fear leads to the behavioral response of freezing.

However, as indicated earlier, we really can't be certain of what is taking place within the phenomenology of the mouse. The mouse might be experiencing fear, but, as well, the mouse also might be experiencing a phenomenology of vigilance, avoidance, stress, shock, and/or pain along side of the fear or instead of such fear.

If shocked for a sufficiently long period of time with no possibility of escape, the mice also might come to exhibit the same sort of 'learned helplessness' that Martin Seligman discovered occurred with respect to dogs when they were exposed to inescapable shocks. Under such circumstances, the freezing might be a sign of learned helplessness rather than a state of fear per se.

Learned helplessness is a more complex phenomenological state than fear since it consists of the integration of a set of experiences rather than being a function of just one experience. Yet, the differences in phenomenological state between fear and learned helplessness both might end up being manifested through the same freezing behavior.

Ramirez and Liu arrange for the genetically engineered channelrhodopsin switch to be activated through the application of a pulse of laser light. This sets in motion a series of cellular biochemical and physiological changes, and, then, freezing behavior is exhibited.

What actually has happened? Has a memory been activated and, then, that memory causes freezing behavior to appear?

Even if it is the case that a certain memory has, somehow, been activated through the activation of the channelrhodopsin switch, can one be sure that the biological situation is not unlike a television set which has been switched on, and, yet, the picture which appears is not – strictly speaking – caused by the turning on the television set. Rather, the turning on of the television set is little more than a necessary precursor for gaining access to a picture (memory) that is generated through an entirely different process occurring outside of the electronic circuits of the television set.

Does the laser-activation of those cells that were active during the process of memory formation (when the unfortunate mice were shocked) represent the recall of a specific kind of memory? Or, does the laser-activation of such cells merely set in motion a sort of 'learned reflex arc' or 'behavioral circuit' that results in freezing behavior without the middleman of memory mediating between laser pulse and the condition of freezing?

We see the pulse of laser light being applied. We see the freezing behavior.

Ramirez and Liu hypothesize that the two events are bridged by the experience of a memory of a specific kind that has been activated by a pulse of laser light. However, they are unable to provide a plausible explanation that can take one step-by-step from the point of initiation (laser stimulation) to the terminal point of behavior and show that what was transpiring involves a memory of a certain kind and the existence of that specific memory caused the observed behavior.

The fact of the matter is that Ramirez and Liu can't even be certain what kind of memory was laid down during the process of shocking. They claim the memory is one of fear, but they can't prove this because they can't eliminate the possibilities

that the memory that formed might have contained elements of stress, pain, shock, and indecision, and not just fear.

Or, perhaps, fear was not part of the original memory phenomenology at all. After all, one might argue that the original memory was one of pain, not necessarily fear, and, therefore, fear is a secondary emotional response to the perception of pain.

Did the laser-activation of cellular activity give expression to a memory of pain rather than fear? If so, then the title of their *Nature* article is, at best, misleading, and at worse, it is incorrect.

Moreover, if the original memory was of pain, then, how does the secondary event of fear come into the picture? How does laser-activation of a pain memory bring about an emotional response of fear that, in turn, brings about freezing behavior? Is the experience of fear a second memory different from the memory of pain, and isn't it possible that pain might be associated with other secondary phenomenological states (e.g., stress, flight, fight, vigilance, and shock) that could just as easily lead to a freezing response?

Ramirez and Liu can see into the structure of their experimental situation only a little farther than their laser-activation of the channelrhodopsin. They know that such activation will set in motion a cascade of biochemical and physiological changes (the sort of changes explored by Eric Kandel and others), and they know that those changes will be followed by changes in synaptic connectivity.

However, they really don't understand what any of this actually means other than the fact that, collectively speaking, it is all correlated with memory formation. The rest is all conjecture and speculation.

During the Boston presentation, Ramirez spoke of giving the mouse "a very mild foot shock". One wonders why a mouse would develop a fear memory if the shock were so "very mild"? Clearly, euphemistical language is being used to mask a process that is more painful than the phrase "very mild" might suggest.

Nothing was said during the Ramirez/Liu presentation (by either the researchers or the audience) with respect to the ethical issues entailed by treating animals in the way they were treated during the experiments that were the focus of the TED presentation. This was true both with respect to surgically altering the heads of the mice to accommodate a laser delivery system as well as in relation to shocking the mice, and, so, the ethical issues to which the researchers were vaguely alluding during their presentation involved something else other than the treatment of life forms within the lab.

When I was an undergraduate, I participated in an experiment involving the delivery of shocks, and the nature of the experiment was such that I was the one who delivered the shocks to myself. For me, there was a clear phenomenological difference between those shocks that were very mild and those shocks that were

painful and might lead to a sense of fear, stress, shock, and/or anxiety if they were to continue.

In a rather startling expression of egocentricity, the researchers appeared to be talking in terms of what they considered to be a very mild foot shock, with nary a spoken worry about what the mouse might have thought or felt about the whole affair. Nonetheless, the word that appears in the title of their Nature article is “fear” – the article title didn’t say anything about ‘a very mild shock memory recall ’, but, rather, used the phrase “fear memory recall”.

Presumably, there is a difference in learning and memory formation with respect to different kinds of stimuli. The phenomenology of the experience involving “a very mild foot shock” is likely to be different than the phenomenology of an experience involving a shock deemed to be capable of generating a memory formation of fear.

So, even if one were to accept at face value everything that the two researchers said with respect to the nature of their experiment and the way in which it supposedly tapped into memory formation, there is a question that remains. Was the memory that was established in the mice one of fear, or of a very mild shock, or of something much more complex?

What exactly was in that memory? The researchers claim that the memory was one of fear, but even if this were true, that fear occurred in a context.

In other words, the shocks took place in an experimental apparatus within a laboratory. The air had a smell. The box had a smell. There were sounds. The box had a feel to it. There were visual qualities present within the box. The surgically implanted mechanism had a ‘feel’ to it.

The foregoing context served as horizon to the experience of the shock. The memory was not just a matter of the alleged fear but, as well, the memory involved certain aspects of the context surrounding the shock.

How are the foregoing sorts of contextual factors coded for with respect to either the cascade of cellular activities that occur in connection to memory formation or with respect to the subsequent alterations in synaptic connectivity? This is not an insignificant issue because, as we shall soon discover, it plays an important role within the Ramirez/Liu experiment.

More specifically, according to the two researchers, if one places a mouse that has been shocked in one laboratory box into another, different box, then the mouse will start out by behaving as any mouse tends to do when introduced into a new environment. In other words, the male or female mouse will begin to explore the box and does not exhibit freezing behavior. All of this changes when a laser is used to activate the channelrhodopsin membrane molecule in those cells that have been identified by the injected genetically engineered sensor-switch as having been active during the process of memory formation in the shock phase of the experiment.

When the laser is used to re-invoke the 'fear memory' by changing the three-dimensional conformation of the channelrhodopsin that leads to the flow of ions into the cell and sets in motion a cascade of biochemical and physiological events associated with memory, mice that previously have been shocked will exhibit the freezing response. According to Ramirez and Liu, the mouse is being induced to remember the original experience of fear and responds accordingly – that is, the mouse freezes.

In their Boston presentation, Ramirez and Liu discuss how they have added a few wrinkles to their experimental design. For example, they talk about, first, taking surgically altered and genetically engineered mice and placing them in a blue box, and, then, identifying the cells that are active in the presence of such 'blueness'.

Before proceeding on with an account of the experiment, it seems to be appropriate to pause briefly and ask a question. How does one know that the cellular activity being identified by the researchers through their genetically engineered sensor-switch has to do specifically with blueness rather than some other feature of the experimental set-up, and, moreover, even if one were to accept the idea that the cellular activity has something to do with retaining a memory of blueness, once again, one can raise the question of what, precisely, such activity has to do with memory formation?

How – specifically -- is 'blueness' being encoded via the cascade of cellular events that are occurring during the learning of, or memory formation concerning, blueness, and how does this particular package or set of cellular events translate into unique changes in synaptic connectivity concerning the issue of blueness? Moreover, how is this aspect of learned or remembered blueness separated from, or integrated into, the context of other sensory experiences that form the context surrounding the experience of blueness?

In addition, one might ask why certain cells are selected for the memory of blueness, while other cells busy themselves with the memory of different sorts of sensory modalities. Or, one also might wonder how the work of an array of active cells concerning different facets of a experiential context become integrated to generate a unified phenomenological experience that can be understood in one way rather than another by a given life form? [By way of a personal aside, for reasons obvious and not so obvious, all of this talk about red and blue boxes led to my thinking about the contents of the so-called 'Blue' and 'Brown' books of Ludwig Wittgenstein which I read as an undergraduate].

Now, let's return to the Ramirez/Liu experiments. In the first stage of one of their experiments involving a blue box, nothing happens to the mice. They just get to explore the box.

In the next phase of the experiment, the mice are placed in a red box. While in the red box, a laser pulse activates the cells that were identified as being active during the blue-box experience, and, as well, the mice are given – I am quite certain – a very

mild foot shock to generate a 'fear' memory that is now associated with a re-invoked or recalled memory of the blue box.

In the final state of this experiment, the mice are placed back in the blue box where they have never been shocked. Yet, as soon as the mice are placed in the blue box, they exhibit freezing behavior.

Ramirez and Liu maintain they have created a false memory in such mice. I have a little difficulty understanding how the two researchers arrived at their conclusion.

But, let's deal with first things first. Ramirez and Liu speak about an association being established between two things. On the one hand, there is the re-invoked memory of blueness, and, on the other hand, there is the shock that is given in the red box while the memory of blueness is re-invoked.

There is no false memory that is being created in the foregoing scenario. The association being established is not a false memory, but, rather, it constitutes the blending together of two facets of the red box context – namely, a shock and the experience of blueness.

This is an example of classical conditioning. One takes a stimulus – blueness – and pairs it with another stimulus – shock – to generate a behavioral response – freezing -- that can be initiated by the presence of blueness alone even without a shock being administered, and even though blueness had never before been experienced as being 'fear-stress-shock-pain-avoidance' related.

The mice are not misremembering the original experience of blueness. They have been taught something new during the time spent in the red box … that is, they have been taught how the presence of blue can be threatening, and when the mice are placed back into the environment of the blue box, they are induced to enter into the condition of freezing because of what they learned in the red box.

Beyond the foregoing considerations, there is the problem of understanding the dynamics of association. How does the memory of association work?

Everyone talks in terms of the capacity of various life forms to associate different aspects of experience whether through temporal and spatial juxtaposition. We all know that such a phenomenon is real, and we all note evidence of its presence through a wide variety of circumstances involving human beings and other life forms.

Nevertheless, no one really knows how it works. No one understands the dynamics of association. We only acknowledge the result of that dynamic.

How does the memory of blueness and the memory of being shocked – very mildly -- enter into a new, modified understanding within the context of a the red experimental box that is capable of generating, say, the freezing response in mice? How does what happens in those cells which are active during the formation of a

memory of blueness become intertwined with what happens in those cells that are active during the experience of being shocked?

One might suppose that there are many neuronal cells that are active during any given experience. Why is blueness singled out as the feature that is to be mixed with the sensory experience of being shocked?

Phenomena such as generalization do occur (as is evidenced by my previously noted aside concerning Wittgenstein's Blue and Brown books in which some sort of generalization took place in relation to the blue and *red* boxes of the Ramirez and Liu experiments). Various life forms do transfer certain aspects of learning or memory developed in one context to a broader array of contexts that are in some, as of yet, mysterious way acknowledged or arbitrarily designated as being similar to the original context of learning.

Unfortunately, we don't really know or understand much about how any of this actually works. We see all kinds of correlations, but we have little idea of how everything fits together and generates or causes this or that memory or this or that understanding or this or that belief or this or that instance of learning, and this remains true even with respect to the simplest of cases involving learning and memory formation such as in instances of: habituation, sensitization, association, conditioning, or generalization.

The experiments conducted by Ramirez and Liu really haven't gotten us any closer to understanding the specific dynamics of either memory, learning, or how the phenomenology surrounding such experience arises. More specifically, their work hasn't helped to show us how to bridge the gap between, on the one hand, changes in the internal biochemistry or physiology of neurons and synaptic connectivity, and, on the other hand, the actual, causal dynamics of learning and memory as a function of the former material changes, nor are we able to explain in a plausible, consistent, rigorous, coherent fashion how changes in neurons and synaptic connectivity become manifested in phenomenological, conscious states that are characterized by differential qualities that are integrated into a unitary sense of experience concerning reality – and quite independently of whether such unified phenomenology actually accurately reflects the nature of some aspect of that reality.

Ramirez and Liu only have provided us with some more correlations. These might be interesting correlations, but, in the end, that is all they are.

The methodological techniques that have been devised and are used to demonstrate the existence of certain correlations are quite innovative. Nonetheless, the bottom line on all this ingenious innovativeness is that nothing which they have said in their TED talk or in corresponding articles gets us any closer to understanding how the dynamics of memory and learning work, and, certainly nothing which they have said demonstrates the truth of the underlying philosophical premise that mind can be shown to be a function of purely material events –- events that can be tinkered with.

This leads to a further issue. Toward the end of the Boston TED talk, Xu Liu talked about how we are living in very exciting times in which science is not tied down by any arbitrary limits with respect to progressing in our understanding and knowledge concerning such phenomena as memory and learning. In effect, science is bound only by our imaginations.

Unfortunately, the imaginations of some people are more problematic and disturbing than are the imaginations of other people. The Defense Department subsidizes a great deal of the scientific work that is taking place in academia and in the corporate sector (both are integral parts in the military-industrial complex), and, as luck would have it, the people who are in control of that Department imagine all kinds of things with respect to the arbitrary uses to which scientific research can be put -- uses that end up killing, maiming, hurting, and enslaving people … both foreign and domestic.

Although the research of Ramirez and Liu has not demonstrated the generation of false memory, that research has revealed some possible techniques for interfering with the minds of life forms. How long will it be before the research of people like Ramirez and Liu is weaponized and applied against whomever the people in power deem to be appropriate.

We don't live just in the exciting times about which Liu enthuses. We also live in very perilous and authoritarian times … times in which all too many governments are quite prepared to do whatever is necessary to stay in power, control resources, and induce citizens to serve that power. Ramirez and Liu are very naïve if they believe their research is only about scientific progress, and they also are in denial if they suppose that they do not have a moral responsibility with respect to the possible applications of their work.

Speaking vaguely about the ethical implications and ramifications of their research work after the fact has got things backward. They should have been concerned about those implications before they did their research, and, in fact, those ethical deliberations should have impacted their decision about whether, or not, such research should have been undertaken at all.

The Ramirez/Liu research dredged up memories within me of Michael Crichton's book: 'The Terminal Man'. Like the scientists in the book, neuroscientists today are full of all kinds of swagger and arrogance with respect to their technical proficiency and ingeniousness, and, unfortunately, like the scientists in Crichton's book, they are ignorant of their own ignorance concerning the many lacunae between what they believe they know and the actual nature of reality.

The scientists in Crichton's book believed they knew what they were doing. They didn't, and their ignorance cost the lives of quite a few people.

The neuroscientists of today believe they know what they are doing. They don't, and the problematic ramifications of that ignorance might only manifest itself after difficulties or tragedies of one kind or another arise.

The many physicists who worked on the Manhattan project believed they knew what they were doing. Few of them grappled with the horrors of Hiroshima or Nagasaki before the fact except, perhaps, Oppenheimer who quoted from the Bhagavad-Gita after witnessing the Trinity test: "Now I am become Death, the destroyer of worlds".

There were many physicists and other scientists who worked to bring nuclear technology into the real world. Those scientists seem unconcerned – before the fact -- about the possibilities of Three Mile Island, Chernobyl, and Fukushima becoming future realities, or about the problems surrounding the disposal of nuclear wastes, or the use of depleted uranium as weapons of mass destruction.

T.S. Eliot said: "Where is the wisdom we have lost in knowledge? Where is the knowledge we have lost in information? Ramirez and Liu, along with a great many other researchers have a lot of information but do not seem to have much in the way of either knowledge, or more importantly, wisdom.

More specifically, I worry about people – such as Ramirez and Liu – who believe they understand what is going on with their experiments when this is just not the case and which, I believe, the foregoing discussion has helped to demonstrate. We already have seen the terrible consequences that have ensued, and are continuing to ensue, from the self-serving arrogance of the pharmaceutical industry with respect to its psychoactive concoctions that are based on a form of technical wizardry that is entirely devoid of any real understanding concerning the human mind, but, is, instead, rooted in a bevy of correlations which are not understood, and, yet, recklessly, the pharmaceutical industry and the FDA are permitting – if not rushing -- all manner of drugs into the market that are generated through spurious science in their attempt to create life-time dependencies (rather than cures) with respect to this or that psychoactive drug.

As people such as Joanna Moncrieff (The Myth of the Chemical Cure) a psychiatrist from England, and Peter Breggin (Medication Madness), a psychiatrist from the United States, have pointed out, neuroscientists have very little understanding of how psychoactive drugs metabolize within human beings or how the actual dynamics of their 'effects' transpire. The existence of side effects lends support to the foregoing claim.

I know of no pharmacological study that begins with a set of predictions concerning the precise array of side effects that will arise in conjunction with the use of a given psychoactive agent. They do not make such predictions because they don't actually know what happens in people when such drugs are taken.

For instance, there are many scientists and clinicians who speak in terms of the idea of "chemical imbalances' being the cause of various emotional and mental problems, and this mythology is present in the marketing campaigns for an array of pharmaceutical products being advertised on television. Let's consider the case of SSRI – that is, selective serotonin re-uptake inhibitors.

I don't know of any neuroscientist who has provided a convincing argument about how the absence of serotonin causes depression or how the absence of serotonin leads to the sorts of symptoms that are associated with clinical depression. Moreover, there is also the rather embarrassing fact that when independent, double blind studies are done concerning the efficacy of SSRIs, those drugs have been shown to be no more effective than placebos.

To whatever extent pharmaceutical agents 'work', they do so by masking problems, not curing them, and in the process, those psychoactive agents dull, if not destroy, many facets of emotional life, awareness, and human sensitivity. Unfortunately, the losing of one's humanity is confused with the alleged effectiveness of a given drug with respect to a change in a user's symptom profile.

Scientific methodologies are one thing. Conjecturing about the significance and meaning of the experimental results that are run through those methodologies is quite another issue altogether.

Ramirez and Liu do not have a theory of memory or learning. They have a series of conjectures based on a problematic understanding concerning, and interpretation of, the correlational dimensions of their own experiments and the experiments of other individuals working in the area of mind/brain research.

The issue before us is the following one. Are neuroscientists on the right track with respect to their attempt to reduce mental phenomena to some set of physical dynamics and, therefore, the work of researchers like Ramirez and Liu represent important steps along an inevitable path that will take us to the promised land of full understanding and a complete explanatory account of how mental phenomena are all functions of underlying biological events? Or, alternatively, are neuroscientists on an asymptote path that generates ever more tantalizing correlations which will never permit them to reach the promised land of complete explanations and, instead, will permit them to only provide accounts of mental phenomena that will always be inherently flawed because there are more realities in heaven and earth, Horatio, than can be dreamt of in their philosophies.

I believe the foregoing critical analysis of the Ramirez and Liu experiments leads to more than a few questions about just what it is that neuroscientists know with respect to the nature of mental phenomena such as memory formation. Maybe, eventually, they will reach the promised land of 'Full Explanations', but right now they are stuck in the entangled underbrush that populates the land of descriptions that are based on proliferating correlations, and they don't seem to have much, if any, real understanding, knowledge, or wisdom concerning the actual nature of the mind.