cogent psychology

COGNITIVE SCIENCE & NEUROSCIENCE | REVIEW ARTICLE

Association, prediction, and engram cells in creative thinking

Dingcheng Yang[1] and Bin Li[1,2]*

*Corresponding author: Bin Li, Washington Institute for Health Sciences, 4601 N Fairfax Drive, Arlington, VA 22203, United States; Department of Neurosciences, Georgetown University Medical Center, 3800 Reservoir Rd NW, Washington, DC 20007, United States
E-mail: bl444@georgetown.edu

Abstract: Creative thinking can be defined as a form of neural processing in the human brain that develops a novel and valuable unity between different or remote percepts or concepts. Recently, experimental studies have demonstrated that the connections made between engram cells or associative memory cells through synaptic plasticity are the neural substrates of memory. Considering the concept of cell assembly, which conjectures that a special group of neurons that connect together and fire simultaneously or sequentially is the neural basis for a percept, memory, or concept, we propose herein that when we acquire a new percept or learn a new concept, a group of new engram cells and their associated circuits will be formed in the brain. We postulate that creative thinking is a form of neurophysiological processing in which a new engram cell group encoding a novel design, concept, or idea arises through the formation of novel connections and/or modulates associations between already existing engram cell groups representing preexisting percepts, memories, or concepts. Aspects of associative and predictive processing are the key components of this proposed mechanism of creative thinking and memory formation.

Subjects: Neuroscience; Cognitive Neuropsychology; Cognitive Science

Keywords: creative thinking; engram cells; associative memory cells; association; prediction

1. Introduction

From the time when "God created Adam" to the moment Apple Inc. claimed the top spot in the world market, creativity has played a paramount role in every aspect of human experience and

ABOUT THE AUTHORS

Bin Li, MD, is a research specialist in the Department of Neurosciences at Georgetown University Medical Center, Washington, DC, and a scientist at the Washington Institute for Health Sciences, Arlington, VA. He received his MD from Hebei Medical University, China. His research interests include neuropharmacology, neurodegenerative diseases, and cognitive psychology. He has published more than 30 articles in peer-reviewed journals and has reviewed manuscripts for multiple journals.

Dingcheng Yang is a research intern at the Washington Institute for Health Sciences, Arlington, VA, and Georgetown University Medical Center, Washington, DC. He made a significant intellectual contribution to this project.

PUBLIC INTEREST STATEMENT

Creativity is and has been humanity's most useful ability for thriving on earth. Artificial intelligence has gradually become one of the hottest topics in science and engineering over the last decade. However, knowledge of the neuropsychological mechanisms of creative thinking is quite limited. In this article, we postulate a new cellular-level model to explain the processes of creative thinking. We believe that this new model could provide further inspiration for the development of computational creativity, a promising subfield of artificial intelligence.

cogent · oa

society, and it will continue to do so in the future. Creativity is and has been humanity's most useful ability for thriving on earth. Fundamentally, without the capacity to think creatively, human beings would not be capable of producing food, building houses, manufacturing cars, creating art, playing sports, and so on. Human life would therefore be just as stereotyped and relatively undynamic as the lives of other animal species. Fortunately, we have obtained creativity over several million years of evolution, and this has provided countless benefits to our species—most importantly, dominance over earth.

Creativity is famous, as well as notorious, for the complexity of and debate over its definition, as creativity encompasses so many aspects that it is difficult to exactly surmise a core concept of it. According to the Oxford English Dictionary, creativity is defined as the capability to create or the creative power or faculty (Simpson & Weiner, 1989). While many researchers have developed their own definitions, some believe creativity is the production of novel and proper work (Jordanous, Keller, & Csermely, 2016). Others believe that the foundation of creativity is the ability to generate surprising and valuable ideas (Beaty, Benedek, Silvia, & Schacter, 2016). Although the majority of people associate creativity with "novelty," Bronowski described the term from another perspective: "the ability to find unity in what appears to be diversity" (Bronowski, 1972). Based on this point of view, Heilman defined creativity as "the new discovery or understanding, development, and expression of orderly relationships" (Heilman, 2016). Therefore, creative thinking can be defined as processing in the human brain that develops novel and valuable designs or concepts through the unification of different or remote percepts or concepts.

Kanematsu and Barry identified three core elements of creativity: creative people, creative products, and the creative process. A creative person is someone vibrant and smart; a creative product is something that never existed before, like a new game or song; and the creative process is the act of a creative person producing a creative product. The creative process as described by Kanematsu and Barry refers to a broad and dynamic interactive framework that includes creative people and their natural and social environments (Kanematsu & Barry, 2016). Theories related to the creative process include investment theory (Sternberg, 2006), action theory (Glaveanu et al., 2013), and honing theory (Gabora, 2017). However, in this article, we only discuss a relatively narrow aspect of the creative process—namely, creative thinking, which takes place exclusively within an individual's brain.

In this paper, we first review published theoretical models of creative thinking and detail how and why we have come to believe that these theories either assert or imply that the processing of associations and predictions in the brain is the critical component of creative thinking. Various associations between different or remote percepts or concepts appear when a person is immersed in creative thinking, and predictive processing occurs simultaneously to select a novel and valuable combination. Next, we examine the relevance of creative thinking theory to neuroscientific findings on the memory engram and the evidence for associative and predictive processing in the brain. We then present a new hypothesis of creative thinking in which we speculate that creative thinking is a neurophysiological process that involves the formation of new engram cell groups, which represent novel designs, concepts, or ideas. The formation of new engram cell groups is dependent on synaptic plasticity. The novel connections or associations between preexisting engram cell groups, namely those representing existing percepts and concepts, are induced, promoted, and consolidated by associative and predictive processing. Finally, we discuss approaches that may be used to test this hypothesis, including molecular functional magnetic resonance imaging (fMRI) technology and computational modeling, as well as the possible applications of this hypothesis in artificial intelligence (AI).

2. The theories about creative thinking: a historical perspective

To understand the mystery of human creativity, many theories have been proposed. In 1926, Wallas proposed that there are four main stages that comprise the process of creative thinking: preparation, incubation, illumination, and verification. During the preparation stage, the brain will

accumulate useful resources for the later creation of new ideas. The processing of associations happens when incubation takes place. Incubation sometimes appears unconsciously to people. This is the "combinatory play" conceived by Einstein. Next comes the illumination stage, defined as an instantaneous "flash" that is always conceived as the peak of a successful trial of association, which was perceivably preceded by a series of unsuccessful and tentative trials. The last stage (verification) involves checking the validity of an idea and reducing it to a precise form (Wallas, 1926). The illumination and verification stages rely on predictive processing, which allows people to forecast the value of a new idea based on experience and knowledge.

In the 1950s, Guilford proposed the concept of divergent thinking. Divergent thinking is the ability to generate multiple solutions to a problem and is characterized by a spontaneous and self-generatable process. Guilford also referred to divergent thinking as synthetic thinking, as it requires the ability to draw on ideas from across disciplines. Thus, divergent thinking is also a form of associative processing (Guilford, 1967).

In 1960, Campbell suggested that creative thought should be seen as a blind-variation and selective-retention process (BVSR) (Campbell, 1960). In addition, Simonton proposed that creativity is largely affected by the capacity to produce blind combinatorial variations, which suggests that it is possible to translate the BVSR theory of creativity into combinatorial (i.e., associative) models (Simonton, 2010). Dietrich et al. later expanded on this theory by applying two paradigms: the evolutionary framework and the emerging prediction framework. According to Dietrich and Haider, blind variation generates ideas, and selective retention determines their usefulness. They proposed that the transition from variation to selection depends on the predictive nature of our brains. In other words, prediction is not only able to give directions to the brain about ideational options but also establishes standards for selection (Dietrich & Haider, 2015).

Indeed, association has been mentioned in many different theories as an important factor for creativity. In 1890, James suggested that combinations of elements and associations are required for creativity to appear. In 1930, Spearman indicated that creativity is a process that combines two or more ideas that were previously isolated (Heilman, 2016). In 1962, Mednick proposed the associative theory under which creative ideas arise spontaneously through associative processes rooted in semantic memory (Mednick, 1962). He cited the French mathematician Poincaré: "ideas rose in crowds; I felt them collide until pairs interlocked so to speak, making a stable combination." Poincaré also argued that the establishment of the existence of a class of Fuchsian functions was stimulated by that odd yet useful combination. Mednick concluded that the more unrelated the ideas combined during the creative thinking process are, the more useful the ultimate outcome of that creative process. After association, the first step in creative thinking, selection of the right combination will occur accordingly. Therefore, Medick proposed that selections are based on the problems themselves. All problems have their unique set of requirements. If the consequences of the combination fit the requirements of the problem, that combination is selected. In other words, the process of evaluating whether a combination fits the requirements can be regarded as predictive processing. In 1964, Koestler proposed the bisociation theory, he believed that the blending of elements that were previously distant to each other is caused by a process involving comparison, abstraction, categorization, analogies, and metaphors (Koestler, 1964). Thus, the bisociation theory also emphasizes the role of association in creativity.

In 1992, Finke et al. established the "Geneplore" model, which depicts creativity in terms of two phases: a generative phase and an exploratory phase. During the generative phase, various forms of information based on previous experiences and knowledge are retrieved and further associated to form many potential ideas called preinventive structures. During the extensive exploratory phase, preliminary ideas will be evaluated, selected, elaborated, and modified based on real-world constraints. According to Finke, the creative process presents a cycling between the two phases (Finke, Ward, & Smith, 1992), which also could be considered an association and prediction cycle.

In 2010, another theory called the explicit–implicit interaction theory was established, paving the way for a novel understanding of creative problem-solving. The five principles underlying this theory are (1) the similarities and differences between explicit and implicit knowledge, (2) the cooperation between explicit and implicit processes, (3) the overlapping representation of explicit and implicit knowledge, (4) the combination of the results of explicit and implicit processing, and (5) iterative processing. The interactions between explicit and implicit processes are crucial for the understanding of this theory. However, explicit processing is related to the preparation and verification stages, namely, the predictive process; implicit processing is related to incubation, namely, the associative process (Hélie & Sun, 2010).

A more recently introduced controlled-attention theory posits a top-down process in which creativity has the ability to control attention and cognition. The theory itself is very much self-explanatory: controlled processes generally occur during creative idea production. They are often goal-directed, aiming for spectacular ideas. However, according to controlled-attention theory, the brain will consciously interfere with these "plain" ideas and move on to come up with some more interesting associations (Beaty, Silvia et al., 2014). This type of control is thus called cognitive control. To make this concept clear, first the brain works on a predictive basis. Second, the predictive processes are used by controlled attention to prioritize information (Schröger, Kotz, & SanMiguel, 2015). Therefore, the controlled-attention theory is mainly based on the predictive nature of the brain.

In 2014, Wiggins and Bhattacharya, after reviewing a wide range of factors, argued that preconscious creativity happens prior to conscious creativity. Unconscious thought is the key to connecting remote and incomplete memories with current issues, creating different potential associations. Wiggins believed that creativity results from the mechanism of adaptive prediction. The foundation of brain function is prediction, not reaction (Wiggins & Bhattacharya, 2014).

In 2016, Pétervári et al. surmised that there are essentially two widely accepted operations of the creative problem-solving process: the manufacture of ideas and the selection of outcomes (Pétervári, Osman, & Bhattacharya, 2016). Based on what has been discussed above, we believe creative thinking is mainly carried out by the processing of association and prediction. Hence, the dynamic interactions between association and prediction are the critical components of creative thinking.

3. Engram cells and a new hypothesis of creative thinking

Although the theories described above put forward some overall concepts for understanding creative thinking, neuroscience requires us to draw a clear picture of the neural mechanisms for creative thinking at the cellular level. The study of creative thinking belongs to cognitive psychology, which studies how people perceive, learn, remember, and think about information (Sternberg & Sternberg, 2011). Memory is one of the two main starting points for creative thinking, the other being perceptual input (Wiggins & Forth, 2015). It is generally believed that memory exists in the form of changes in the connections between neurons. In humans, there are trillions of connection points, also known as synapses, which constitute the physiological units of memory. Plasticity of this massive quantity of neurons and synaptic connections is critical for information storage and memory and is mediated mainly by strengthening and weakening of synaptic connections through long-term potentiation (LTP) and depression (LTD), respectively (Camina & Güell, 2017; Stanton & Sejnowski, 1989). Via these mechanisms, the strength of synapses will be adjusted accordingly through LTP and LTD whenever a piece of information flows across neurons. This is the widely accepted Hebbian synaptic plasticity theory (Hebb, 1949).

Another important theory of memory is the memory engram theory introduced by Richard Semon in 1904. Memory engram cells are "a population of neurons that are activated by learning, have enduring cellular changes as a consequence of learning, and whose reactivation by a part of the original stimuli delivered during learning results in memory recall" (Tonegawa, Liu et al.,

2015a). Memory engram cells and circuits have recently been identified in mouse hippocampus and amygdala using novel technologies that label and trace memory engrams over time and in response to particular experiences or neurophysiological manipulations. Specifically, memory engram technology is a combinatorial approach involving integration of transgenic, optogenetic, and pharmacogenetic technologies along with memory training experiments. For example, genetic engineering techniques in mice can be used to tag cells expressing immediate early genes (e.g., *c-fos* or *arc*), which are markers of neuronal activity, during contextual fear conditioning (a memory training experiment), and then specifically induce the expression of channelrhodopsin-2 in activated neurons. Channelrhodopsin-2 is a retinylidene protein that functions as a light-responsive cation-selective ion channel; thus, upon activation by light, cations flow through these channels and can induce an action potential (Nagel et al., 2003). When these labeled neurons were activated by blue light through optic fibers mounted on the brain, mice showed conditioned freezing behavior even in the absence of the cue. In control experiments, conditioned freezing behavior was not observed in non-fear-conditioned mice, although they also expressed channelrhodopsin-2 in a similar proportion of neurons. These studies provided direct evidence that memory engram cells and circuits are the substrate of memory information storage (Liu et al., 2012; Tonegawa, Pignatelli et al., 2015b).

In cross-modal reflex experiments, paired odor and whisker stimulations were applied to establish whisker-induced olfactory responses and odorant-induced whisker motion in mice. These studies suggested that associative memory cells may be located in sensory cortices, where they may carry out storage and retrieval of multiple associated signals by establishing mutual synaptic innervations among coactivated sensory cortices (Wang & Cui, 2017). It is thus reasonable to believe that associative memory cells and memory engram cells are the same kind of cells. Wang et al. also speculated not only that the association of endogenous signals could induce the formation of primary associative memory cells in sensory cortices but also that associative thinking and logical reasoning could promote the formation of new high-level associative memory cells through connections of different primary associative memory cells with mutual synapse innervations. They summarized their hypothesis as follows: "the more associative thinking is, the higher the integration of associative memory cells and the more inspiration there is" (Wang & Cui, 2017).

Memory engram theory can be integrated with the concept of cell assembly first introduced by Hebb in 1949. Hebb's cell assembly model claims that a special group of neurons that connect together and fire simultaneously or sequentially is the neural basis for a percept, memory, or concept (Hebb, 1949; Huyck & Passmore, 2013). Based on (1) theories of creative thinking, (2) recent discoveries and characterizations of memory engram cells, and (3) the concept of cell assembly, we herein propose a new hypothesis of creative thinking.

First, we propose that a special group of engram cells (or memory associative cells) forms a special cell assembly, which represents a percept, memory, or concept. When we acquire a new percept or memory or learn a new concept, a group of new engram cells or memory associative cells will form in our brains. The associated engram cells or memory associative cells in this special group are probably distributed over broad cortical areas and certain subcortical areas rather than in a special brain region.

Second, we propose that creative thinking can be defined as processes of the human brain that develop novel and valuable unities between different or remote percepts or concepts. Therefore, we speculate that creative thinking is also a neurophysiological process, similar to learning, which involves the formation of new engram cell groups representing novel designs, concepts, or ideas. The formation of new engram cell groups is a process that connects or associates preexisting engram cell groups that represent previously acquired percepts and concepts. This processing is also dependent on synaptic plasticity.

Third, we consider how the new engram cells are grouped and how neural representations of a new design, concept, or idea can form without learning or training from the external environment. We postulate that associative processing and predictive processing in the brain are the critical mechanisms that induce, promote, and consolidate the connections between relevant neurons during the formation of new engram cell groups when we think creatively. In short, creative thinking is the result of neurophysiological processing dependent on association and prediction in which a new engram cell group representing a creative idea is formed.

The smartphone, as an example of a creative product, is useful for explaining this hypothesis. A smartphone combines a series of individual electronic devices, such as a wireless phone, personal computer, internet, camera, and GPS navigator. From a neurophysiological view, the physiological basis of every percept, memory, or concept is based on relevant groups of engram cells in the brain. In the process of creative thinking, the engram cell groups representing distinct concepts such as personal computers, wireless phones, and cameras are associated with each other. After acknowledgement of the value and realizability of such associations during predictive processing, this group of interneurons (engram cells) will establish a solid connection with existing engram cell groups representing the disparate concepts and then coordinate these engram cell groups to form a new engram group that encodes the design for a smartphone that incorporates the disparate concepts.

The free energy principle, which is based on the characteristic of biological systems that have a motivation to resist a natural tendency to disorder, has been applied as an important global theory of how the brain works. Minimization of prediction error or avoidance of surprise is the motivation of the brain (Friston, 2010). During the processing of creative thinking, a broad and random association among different percepts, memories, and concepts (i.e., a brainstorm) appears in the brain in a high-entropy state. The brain actively predicts these temporary associations, and when an ideal combination meets a merit criterion, the prediction error is minimized. This special association representing a creative idea is then consolidated, which means a group of new engram cell groups is formed, and the brain returns to a low-entropy state.

4. Neuroscientific findings on associative and predictive processing in creative thinking

Since association and prediction are critical for the process of creative thinking, it is important to consider the experimental evidence linking these two neurophysiological processes with creative thinking. First, neuroscientific studies have demonstrated that intra- and interhemispheric connectivity, which are related to association, play key roles in creativity. Jausovec et al. found that electroencephalographic (EEG) coherence was related to the level of creativity needed to solve a problem. Noticeable increases in intra- and interhemispheric cooperation mainly between distant brain regions were observed in the EEG activity of respondents solving dialectic problems. These results are explained by the more intense involvement of the long-range corticocortical fiber system in creative thinking (Jausovec & Jausovec, 2000). Jausovec et al. also investigated the differences in EEG coherence among gifted, creative, and intelligent subjects and individuals of average ability when they solved closed and open problems. They found that highly intelligent individuals showed more cooperation between brain areas when solving closed problems than did individuals of average intelligence. Moreover, highly creative individuals showed more cooperation between brain areas than did highly intelligent individuals when solving open problems (Jausovec, 2000).

Takeuchi et al. used diffusion tensor imaging and a behavioral creativity test of divergent thinking to investigate the relationship between creativity and structural connectivity. They examined associations between creativity and fractional anisotropy, which reflects nerve fiber density, axonal diameter, and myelination in white matter, across the brain in healthy young adults. Significant positive relationships between fractional anisotropy and individual creativity were observed in some white matter areas, such as the body of the corpus callosum and the bilateral temporoparietal junction. These results are congruent with the idea that creativity is associated with the integration of conceptually distant ideas held in different brain domains and architectures (Takeuchi et al., 2010). Further supporting this concept, Wu et al. constructed a brain white matter network structure that consisted

of cerebral tissues and nerve fibers in 35 healthy adults and used graph theory to examine the relationship between the connectivity efficiencies and creativity of the brain regions with diffusion tensor imaging. The results confirmed that creativity is based on efficient integration and connectivity between different regions of the brain (Wu, Zhong, Chen, & Wennekers, 2016).

In functional imaging studies, Takeuchi et al. used resting-state fMRI (Rs-fMRI) and a creativity test to investigate across-subject correlations between scores on a divergent thinking test and resting-state functional connectivity between the medial prefrontal cortex and other brain regions. The results indicated that higher creativity is associated with stronger resting-state functional connectivity between the medial prefrontal cortex and default mode network (Takeuchi et al., 2012). Wei et al. also confirmed that creativity measured with the Torrance tests of creative thinking was positively correlated with the strength of resting-state functional connectivity between the medial prefrontal cortex and the middle temporal gyrus measured with Rs-fMRI (Wei et al., 2014). Beaty et al. used Rs-fMRI as well and found that the ability to generate creative ideas was characterized by increased functional connectivity between the inferior prefrontal cortex and the default network (Beaty, Benedek et al., 2014). Overall, these EEG, neuroimaging, and behavioral studies indicate that creative thinking is dependent on anatomical connectivity between different brain regions.

As we discussed above, our brains can generate many novel ideas by associative processing unconsciously or intentionally during creative thinking. However, how do brains manage to select creative ideas, and what is the neural mechanism for this process? To answer these questions, Dietrich and Wiggins et al. proposed that selection is dependent on the prediction machinery of the brain (Wiggins, 2014; Dietrich & Haider, 2015). Clark proposed that brains are essentially prediction machines. There are essentially infinite sensory inputs into the brain at any time. In order to make behavior purposeful and timely, brains must constantly match these inputs via top-down information encoding expectations or predictions to identify and select meaningful information. Perception, recognition, learning, memory, attention, and motor functions are all involved in the predictive process (Clark, 2013).

Bach et al. studied the mechanism of predicting future reward using magnetoencephalography and found that a representation of "predicted mean reward" emerges early in the parietal/sensory regions and later in the frontal cortex. "Predicted reward variability representations" (i.e., economic risk) appear in most regions simultaneously, and slightly later than "mean reward." These findings provide insight into how a dynamic encoding of probabilistic reward prediction unfolds in the brain in both time and space (Bach, Symmonds, Barnes, & Dolan, 2017).

Roberts et al. used fMRI to investigate the neural correlations underlying the association between cognitive flexibility and future prediction. They found that individual differences in cognitive flexibility were associated with differences in activity of some regions in the frontoparietal control network (including the rostrolateral prefrontal cortex, middle frontal gyrus, anterior insula/frontal operculum, dorsal anterior cingulate cortex, precuneus, and anterior inferior parietal lobule), salience network (the key nodes of which are in the insular cortex), and the default mode network (including the medial prefrontal cortex, posterior cingulate cortex, lateral and medial temporal lobes, and posterior inferior parietal lobule) during a future prediction condition (Roberts et al., 2017).

Although there is no direct neuroscientific evidence showing important roles of predictive processes in creative thinking, Dietrich et al. proposed that the brain's predictive mechanisms can give direction to the production of ideational combinations and selection in the creative process, which is dependent on the prediction of merit criteria. They postulated that "Emulation chaining over many iterations might underlie the scaffolding effect that enables thought trials to leap over unrealizable forms." Therefore, we can presume that associative and predictive processing is critical in creative thinking.

5. Cellular-level brain imaging, computational modeling, and computational creativity

Our hypothesis is intended to explain the neural mechanisms of creative thinking at the cellular level. However, creative thinking is a unique neurophysiological activity of humankind that involves

interactions between enormous numbers of neurons. Developing experimental methods for noninvasively probing the unique and staggeringly complex orchestration of creativity-related physiological activity at the cellular level in human subjects, as is necessary to test our hypothesis, is a tremendous challenge. Current functional brain imaging techniques, such as MRI and positron emission tomography, are far from capable of accomplishing this task because of their low spatial and temporal resolution and lack of specificity for well-defined neural events. However, a new emerging molecular fMRI technology brings hope in solving this problem. This technology is based on the development of MRI molecular imaging agents to detect neurotransmitters, calcium ions, and gene expression in neurons (Bartelle, Barandov, & Jasanoff, 2016). The theoretical resolution limit of MRI is less than 10 μm, whereas the soma of a neuron is about 4–100 μm in diameter. Thus, it may provide noninvasive functional neuroimaging with molecular specificity to show dynamic pictures of the brain at the resolution of individual cells in animals and, eventually, people. When this technology matures, we may use it to observe the neuronal activity underlying association and prediction during creative thinking. For example, we imagine an experiment in which subjects would think out a creative idea during a cognitive task while we detect new groups of neurons (engram cells) related to the creative idea in specific brain regions. In addition, activation of these cells may be monitored when subjects recall the creative idea. We anticipate that the rapid development of such imaging technologies will permit direct testing of our hypothesis.

In addition to experimental studies, computational modeling is a practical and precise method for describing complex systems that has been integrated into computational neuroscience. Mathematical models of the nervous system can elucidate the principles of information processing and the physiological and cognitive abilities of the brain. To thoroughly understand creative thinking, which may well be the most complex phenomenon in the universe, we need to develop computational models to reveal a clear picture of the neural mechanisms of creative thinking.

Launched in 2005 at the Swiss Federal Institute of Technology in Lausanne, the Blue Brain project aims to build a detailed computer simulation of the brain. The empirical data in this model comprise neurons' 3D shapes, electrical properties, ion channels, and other information (https://bluebrain.epfl.ch/). In 2015, scientists on this project presented the first-draft digital reconstruction of the microcircuitry of a juvenile rat's somatosensory cortex, which has a volume of 0.29 mm^3 and contains approximately 31,000 neurons and 37 million synapses. The reconstruction used cellular and synaptic organizing principles to algorithmically reconstruct detailed anatomy and physiology from sparse experimental data. The researchers found a spectrum of network states with a sharp transition from synchronous to asynchronous activity modulated by physiological mechanisms. The spectrum of network states that were dynamically reconfigured around this transition supports diverse information processing strategies (Markram et al., 2015). One future goal of this project is to establish digital reconstructions of large-scale brain regions, including the cortex, hippocampus, basal ganglia, and cerebellum, and eventually complete the construction and functional simulation of the intact rat brain and, ultimately, the human brain. Since the human brain has approximately 100 billion neurons and 100 trillion synapses, breakthroughs in supercomputer software and hardware are essential to achieving this goal. Furthermore, quantum computers and quantum algorithms developed in recent years may aid the analysis of complex systems (Trabesinger, 2017a, 2017b).

However, a mathematic model only needs to describe certain meaningful aspects of reality, not all of its characteristics. Furthermore, modern computers are capable of processing speeds that match the maximum number of nerve impulses in the human brain (Hilbert & López, 2011). Therefore, in addition to the Blue Brain project and similar large international projects (https://www.humanbrainproject.eu/en/) aiming to reconstruct the brain at an unprecedented level of biological detail, neuroscientists are also studying simplified models with a few parameters, such as the electrophysiological properties of neurons and their associated synapses, to establish a mathematical matrix of the brain. Regardless of the specific models employed, we must successively establish the modes of sensation, perception, learning, memory, attention, emotion, association, predication, etc. from low to high levels and finally establish a brain model capable of simulating ideation. We believe that the principle of

creative thinking will emerge during these works and that the hypothesis presented herein could be verified (Breakspear, 2017; Teufel & Fletcher, 2016).

AI has gradually become one of the hottest topics in science and engineering over the last decade, and AI technology continues to make great advancements. This accomplishment will be another landmark in human civilization, with virtually any potential form of data being processed and analyzed intelligently. AI has been used in a variety of fields, including computer vision, speech recognition, natural language processing, medical diagnosis, bioinformatics, and drug design. Computational creativity, though in an early stage, is a promising subfield of AI that can be used to generate innovative artistic works, scientific theories, mathematical concepts, and engineering designs (Boden, 2015). We expect that computational creativity may become one of the driving forces for accelerating the cultural, technological, medical, and scientific advancement of humanity.

There are many intersections between AI and neuroscience. Hassabis et al. argued for the critical and ongoing importance of neuroscience in generating ideas that will accelerate and guide AI research. Neuroscience can provide a rich source of inspiration for new types of algorithms and architectures, independent of and complementary to the mathematical and logic-based methods and ideas that have largely dominated traditional approaches to AI. For example, AI has been revolutionized over the past few years by dramatic advances in neural network and "deep learning" methods (Hassabis, Kumaran, Summerfield, & Botvinick, 2017). Currently, the best explored processes in computational creativity are artifact generation and selection. Evolutionary mechanisms, analogy models, conceptual associations, and blending have been successfully used to produce creative artifacts, such as music, poetry, visual art, and cookery. We hope our hypothesis of creative thinking can provide further inspiration for the development of computational creativity.

6. Conclusions

In this article, we reviewed the major theories of creative thinking and concluded that the key neural processes in creative thinking are association and prediction. Considering the neuroscientific discoveries on engram cells and the concept of cell assembly, we hypothesized that creative thinking is a form of neurophysiological processing involving the formation of new engram cell groups, which represent novel designs, concepts, or ideas. This processing is induced, promoted, and consolidated by associative and predictive processing during creative thinking. This engram cell hypothesis explains the physiological basis of creative thinking at the cellular level and may be testable with experimental approaches such as molecular fMRI. Additionally, this hypothesis also fits into the free energy principle, which is an important global brain theory. Finally, this engram cell hypothesis may offer inspiration for the development of computational creativity, a promising subfield of AI.

Competing Interests
The authors declare no competing interest.

Author details
Dingcheng Yang[1]
E-mail: ydc168yes@gmail.com
ORCID ID: http://orcid.org/0000-0002-7094-8564
Bin Li[1,2]
E-mail: bl444@georgetown.edu
ORCID ID: http://orcid.org/0000-0002-1051-801X
[1] Washington Institute for Health Sciences, Arlington, VA, United States.
[2] Department of Neurosciences, Georgetown University Medical Center, Washington, DC, United States.

Author Contributions
All authors listed have made substantial intellectual contributions to the conceptualization of the work. DY prepared the original draft. BL completed the review and editing. Final approval of the version to be published was the responsibility of DY and BL.

References
Bach, D. R., Symmonds, M., Barnes, G., & Dolan, R. J. (2017). Whole-brain neural dynamics of probabilistic reward prediction. *The Journal of Neuroscience : the Official Journal of the Society for Neuroscience, 37,* 3789–3798. doi:10.1523/JNEUROSCI.2943-16.2017

Bartelle, B. B., Barandov, A., & Jasanoff, A. (2016). Molecular fMRI. *The Journal of Neuroscience : the Official Journal of the Society for Neuroscience, 36,* 4139–4148. doi:10.1523/JNEUROSCI.4050-15.2016

Beaty, R. E., Benedek, M., Silvia, P. J., & Schacter, D. L. (2016). Creative cognition and brain network dynamics. *Trends Cognition Sciences, 20*, 87–95. doi:10.1016/j.tics.2015.10.004

Beaty, R. E., Benedek, M., Wilkins, R. W., Jauk, E., Fink, A., Silvia, P. J., & Neubauer, A. C. (2014). Creativity and the default network: A functional connectivity analysis of the creative brain at rest. *Neuropsychologia, 64*, 92–98. doi:10.1016/j.neuropsychologia.2014.09.019

Beaty, R. E., Silvia, P. J., Nusbaum, E. C., Jauk, E., & Benedek, M. (2014). The roles of associative and executive processes in creative cognition. *Memory & Cognition, 42*, 1186–1197. doi:10.3758/s13421-014-0428-8

Boden, M. A. (2015). How computational creativity began. In T. R. Besold, M. Schorlemmer, & A. Smaill (Eds.), *Computational creativity research-towards creative machines* (pp. 6–12). Paris, France: Atlantis Press.

Breakspear, M. (2017). Dynamic models of large-scale brain activity. *Nature Neuroscience, 20*, 340–352. doi:10.1038/nn.4497

Bronowski, J. (1972). *Science and human values*. New York: Harper and Row.

Camina, E., & Güell, F. (2017). The neuroanatomical, neurophysiological and psychological basis of memory: Current models and their origins. *Frontiers in Pharmacology, 8*, 438. doi:10.3389/fphar.2017.00438

Campbell, D. T. (1960). Blind variation and selective retention in creative thought as in other knowledge processes. *Psychological Review, 67*, 380–400. doi:10.1037/h0040373

Clark, A. (2013). Whatever next? Predictive brains, situated agents, and the future of cognitive science. *The Behavioral and Brain Sciences, 36*, 181–204. doi:10.1017/S0140525X12000477

Dietrich, A., & Haider, H. (2015). Human creativity, evolutionary algorithms, and predictive representations: The mechanics of thought trials. *Psychonomic Bulletin & Review, 22*, 897–915. doi:10.3758/s13423-014-0743-x

Finke, R. A., Ward, T. B., & Smith, S. M. (1992). *Creative cognition: Theory, research, and applications*. Cambridge: MIT Press.

Friston, K. (2010). The free-energy principle: A unified brain theory? *Nature Reviews. Neuroscience, 11*, 127–138. doi:10.1038/nrn2787

Gabora, L. (2017). Honing theory: A complex systems framework for creativity. *Nonlinear Dynamics, Psychology, and Life Sciences, 21*, 35–88.

Glaveanu, V., Lubart, T., Bonnardel, N., Botella, M., De Biaisi, P. M., Desainte-Catherine, M., … Zenasni, F. (2013). Creativity as action: Findings from five creative domains. *Frontiers in Psychology, 16*, 176. doi:10.3389/fpsyg.2013.00176

Guilford, J. P. (1967). *The nature of human intelligence*. New York: McGraw-Hill.

Hassabis, D., Kumaran, D., Summerfield, C., & Botvinick, M. (2017). Neuroscience-inspired artificial intelligence. *Neuron, 95*, 245–258. doi:10.1016/j.neuron.2017.06.011

Hebb, D. O. (1949). *The organization of behavior*. New York: John Wiley & Sons.

Heilman, K. M. (2016). Possible brain mechanisms of creativity. *Archives Clinical Neuropsychology, 31*, 285–296. doi:10.1093/arclin/acw009

Hélie, S., & Sun, R. (2010). Incubation, insight, and creative problem solving: A unified theory and a connectionist model. *Psychological Review, 117*, 994–1024. doi:10.1037/a0019532

Hilbert, M., & López, P. (2011). The world's technological capacity to store, communicate, and compute information. *Science, 332*, 60–65. doi:10.1126/science.1200970

Huyck, C. R., & Passmore, P. J. (2013). A review of cell assemblies. *Biological Cybernetics, 107*, 263–288. doi:10.1007/s00422-013-0555-5

Jausovec, N. (2000). Differences in cognitive processes between gifted, intelligent, creative, and average individuals while solving complex problems: An EEG study. *Intelligence, 28*, 213–237. doi:10.1016/S0160-2896(00)00037-4

Jausovec, N., & Jausovec, K. (2000). EEG activity during the performance of complex mental problems. *International Journal of Psychophysiology : Official Journal of the International Organization of Psychophysiology, 36*, 73–88. doi:10.1016/S0167-8760(99)00113-0

Jordanous, A., Keller, B., & Csermely, P. (2016). Modelling creativity: Identifying key components through a corpus-based approach. *PLoS. One, 11*, e0162959. doi:10.1371/journal.pone.0162959

Kanematsu, H., & Barry, D. M. (2016). Theory of creativity. In H. Kanematsu & D. M. Barry (Eds), *STEM and ICT education in intelligent environments* (pp. 9–13). Cham, Switzerland: Springer International Publishing.

Koestler, A. (1964). *The act of creation*. New York: Penguin Books.

Liu, X., Ramirez, S., Pang, P. T., Puryear, C. B., Govindarajan, A., Deisseroth, K., & Tonegawa, S. (2012). Optogenetic stimulation of a hippocampal engram activates fear memory recall. *Nature, 484*, 381–385. doi:10.1038/nature11028

Markram, H., Muller, E., Ramaswamy, S., Reimann, M. W., Abdellah, M., Sanchez, C. A., … Schürmann, F. (2015). Reconstruction and simulation of neocortical microcircuitry. *Cell, 163*, 456–492. doi:10.1016/j.cell.2015.09.029

Mednick, S. A. (1962). The associative basis of the creative process. *Psychological Review, 69*, 220–232.

Nagel, G., Szellas, T., Huhn, W., Kateriya, S., Adeishvili, N., Berthold, P., … Bamberg, E. (2003). Channelrhodopsin-2, a directly light-gated cation-selective membrane channel. *Proceedings of the National Academy of Sciences of the United States of America, 100*, 13940–13945. doi:10.1073/pnas.1936192100

Pétervári, J., Osman, M., & Bhattacharya, J. (2016). The role of intuition in the generation and evaluation stages of creativity. *Frontiers in Psychology, 7*, 1420. doi:10.3389/fpsyg.2016.01420

Roberts, R. P., Wiebels, K., Sumner, R. L., Van Mulukom, V., Grady, C. L., Schacter, D. L., & Addis, D. R. (2017). An fMRI investigation of the relationship between future imagination and cognitive flexibility. *Neuropsychologia, 27*, 156–172. doi:10.1016/j.neuropsychologia.2016.11.019

Schröger, E., Kotz, S. A., & SanMiguel, I. (2015). Bridging prediction and attention in current research on perception and action. *Brain Research, 1626*, 1–13. doi:10.1016/j.brainres.2015.08.037

Simonton, D. K. (2010). Creative thought as blind-variation and selective-retention: Combinatorial models of exceptional creativity. *Physics of Life Reviews, 7*, 190–194. doi:10.1016/j.plrev.2010.05.004

Simpson, J. A., & Weiner, E. S. C., & Oxford University Press. (1989). *Oxford English dictionary* (2nd ed.). New York: Author.

Stanton, P. K., & Sejnowski, T. J. (1989). Associative long-term depression in the hippocampus induced by hebbian covariance. *Nature, 339*, 215–218. doi:10.1038/339215a0

cogent ·· psychology

Sternberg, R. J. (2006). The nature of creativity. *Creativity Research Journal, 18*, 87–98. doi:10.1207/s15326934crj1801_10

Sternberg, R. J., & Sternberg, K. (2011). *Cognitive psychology* (6th ed.). Belmont, CA: Wadsworth.

Takeuchi, H., Taki, Y., Hashizume, H., Sassa, Y., Nagase, T., Nouchi, R., & Kawashima, R. (2012). The association between resting functional connectivity and creativity. *Cerebral Cortex, 22*, 2921–2929. doi:10.1093/cercor/bhr371

Takeuchi, H., Taki, Y., Sassa, Y., Hashizume, H., Sekiguchi, A., Fukushima, A., & Kawashima, R. (2010). White matter structures associated with creativity: Evidence from diffusion tensor imaging. *Neuroimage, 51*, 11–18. doi:10.1016/j.neuroimage.2010.02.035

Teufel, C., & Fletcher, P. C. (2016). The promises and pitfalls of applying computational models to neurological and psychiatric disorders. *Brain, 139*, 2600–2608. doi:10.1093/brain/aww209

Tonegawa, S., Liu, X., Ramirez, S., & Redondo, R. (2015a). Memory engram cells have come of age. *Neuron, 87*, 918–931. doi:10.1016/j.neuron.2015.08.002

Tonegawa, S., Pignatelli, M., Roy, D. S., & Ryan, T. J. (2015b). Memory engram storage and retrieval. *Current Opinion in Neurobiology, 35*, 101–109. doi:10.1016/j.conb.2015.07.009

Trabesinger, A. (2017a). Quantum computing: Towards reality. *Nature, 543*, S1. doi:10.1038/543S1a

Trabesinger, A. (2017b). Quantum leaps, bit by bit. *Nature, 543*, S2–S3. doi:10.1038/543S2a

Wallas, G. (1926). *The art of thought*. NewYork: Harcourt Brace.

Wang, J. H., & Cui, S. (2017). Associative memory cells: Formation, function and perspective. *Version 2. F1000Research, 6*, 283. doi:10.12688/f1000research.11096.2

Wei, D., Yang, J., Li, W., Wang, K., Zhang, Q., & Qiu, J. (2014). Increased resting functional connectivity of the medial prefrontal cortex in creativity by means of cognitive stimulation. *Cortex, 51*, 92–102. doi:10.1016/j.cortex.2013.09.004

Wiggins, G. A., & Bhattacharya, J. (2014). Mind the gap: An attempt to bridge computational and neuroscientific approaches to study creativity. *Frontiers in Human Neuroscience, 8*, 540. doi:10.3389/fnhum.2014.00540

Wiggins, G. A., & Forth, J. (2015). DyOT: A computational theory of creativity as everyday reasoning from learned information. In T. R. Besold, M. Schorlemmer, & A. Smaill (Eds.), *Computational creativity research-towards creative machines* (pp. 127–148). Paris, France: Atlantis Press.

Wu, C., Zhong, S., Chen, H., & Wennekers, T. (2016). Discriminating the difference between remote and close association with relation to white-matter structural connectivity. *PLoS One, 11*, e0165053. doi:10.1371/journal.pone.0165053