Chapter 16
Open Questions on Mind, Genes, Consciousness, and Behavior: The Circadian and Ultradian Rhythms of Art, Beauty, and Truth in Creativity

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An earlier companion volume to this text ended with an epilogue on "The Unification Hypothesis of Chronobiology from Molecule to Mind" wherein we traced the evolution of life and mind as manifest in our circadian and ultradian psychobiology (Lloyd and Rossi, 1992). This chapter extends that broad scenario by reviewing the circadian and ultradian rhythms of gene expression, brain plasticity, and creative experience as we pursue the eternal verities of art, beauty, and truth in science as well as everyday life. This will be a highly speculative and lofty philosophical pursuit, which we will survey as a provocative series of "open questions" about mind, genes, consciousness, and behavior. We will explore our understanding of "the meaning of it all" by balancing the traditional reductionism of chronobiological research with the constructive approaches of the new *in silico* bioinformatic databases of functional genomics, neuroscience, medicine, and psychology. We will balance the traditional "Bottoms-Up Approach" of the physical and biological sciences with our "Top-Down Approach" for a unified understanding of the human condition from a deep chronobiological and psychobiological perspective.

Keywords Art, basic rest activity cycle, brain plasticity, gene expression hypnosis, implicit processing heuristic, psychosocial genomics, psychotherapy, truth, ultradian music

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16.1 Open Question #1: Do *In Silico* Models of Computer Research Bridge the Cartesian Gaps Between Mind, Gene, Brain, and Body?

In silico is a popular expression in the computer and bioinformatic approaches to simulating life processes on all levels from mind and behavior to molecular genomics. These simulations of complex life processes are performed via information processing models *on silicon chips* in computers as a more economical approach to experimentation than traditional wetware biological. *In silico* research is the key to *data mining: the exploration, assessment, and integration of the meaning and implications of the research literature in many biological and psychological disciplines that cannot be integrated in any other way*. Such *interdisciplinary in silico research* appears to bridge the awkward Cartesian Gap between mind, gene, brain, and body via the concept of information. The genomic revolution made the concept of information the common denominator of all the databases in the life sciences. The Allen Brain Atlas of Gene Expression (ABA), for example, makes it possible to integreate biology, genomics, and neuroscience in a single database. Of greatest interest is how the ABA could make it possible to explore the circadian and ultradian dynamics of activity-dependent gene expression and brain plasticity associated with psychosocial stress, memory, learning, behavior, cognition, creativity, and consciousness itself (Rossi, 2007).

The Allan Brain Atlas (http://www.brain-map.org) is available free as a web based database showing the location and activity level of ~21,000 genes in the mouse brain, which shares about 90% homology with the human brain. Plans are now underway for making a complete human brain atlas of gene expression. This anatomical reference for understanding the role of gene expression for ~50 million Americans suffering from brain dysfunctions such as Alzheimer's, epilepsy, and Parkinson's as well as addiction, depression, and stress is already being described as the foundation for a new neuroscience of mind, behavior, rehabilitation, and psychotherapy. The Allen Brain Atlas consists of the data of 250,000 microscope slides, a million brain sections, and 85 million anatomical photo files, which are assembled for viewing gene expression in three dimensional cross sections of the brain. An unexpected finding revealed by the ABA is that ~80% of genes are expressed in brain cells. The high-resolution digital microscopy images of the ABA show the exact location of the activity-dependent genes that are expressed to generate the proteins carrying out the biological functions of mind and behavior in health and illness.

At the present time research and publications involving the Allen Brain Atlas http://www.brainatlas.org/aba/ are dominated by basic biology with a heavy focus on drug and medical applications. Of particular interest for bridging the Cartesian mind-body gap, however, is the ABA potential for tracking the activity-dependent genes expressed generating brain plasticity (synaptogenesis and neurogenesis) in response to the normal activities of life, memory, learning, behavior as well as

creative human experiences of art, truth, and beauty. In principle any active psychological experience of art, truth, and beauty that can be located in the brain by functional magnetic resonance imaging fMRI (Liu et al., 2007; Rossi, 2007) can be tracked down to the molecular genomic level via the ABA. Researchers in psychology, however, have had difficulty in recognizing the implications of this mind-molecular bridge because before the advent of fMRI technology there was no obvious and non-invasive way of assessing the deep molecular-genomic sources of cognition, emotion, and behavior. Gene expression is usually measured by complex and very expensive laboratory procedures such as DNA microarrays that involve taking invasive tissue samples from the brain, blood, saliva, and body (Rossi, 2002, 2004, 2005, 2006 et al., 2007). This stumbling block motivates us to outline in Fig. 16.1 how the ABA in association with other currently available technologies may enable us to bypass invasive biological methods with new *In silico* models of exploring the mind-gene connection in psychotherapy.

Figure 16.1 outlines how the bioinformatic technologies of the Allen Brain Atlas of Gene Expression, functional magnetic resonance imaging (fMRI) (Segel et al., 2006), and the Connectivity Map (Lamb et al., 2006) can be integrated into a new *in silico* model of mind, gene, brain, and body communication with nothing more than a personal computer and an internet connection. This type of *In silico* data mining of the existing scientific literature was originally described in a more limited biological context by Blagosklonny and Pardee (2002).

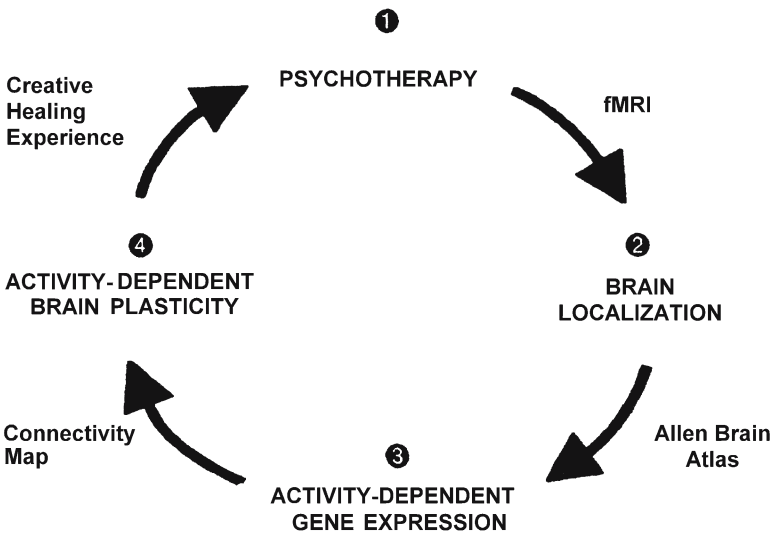

Fig. 16.1 An *In Silico* model for mind-brain-body-gene research that apparently bridges the Cartesian mind-body gap

> Millions of easily retrievable facts are being accumulated in databases, from a variety of sources in seemingly unrelated fields, and from thousands of journals. New knowledge can be generated by 'reviewing' these accumulated results in a concept-driven manner, linking them into testable chains and networks.… Connecting separate facts into new concepts is analogous to combining the 26 letters of the alphabet into languages. One can generate enormous diversity without inventing new letters. These concepts (words), in turn, constitute pieces of more complex concepts (sentences, paragraphs, chapters, books). *We call this process 'conceptual' research, to distinguish it from automated data-mining and from conventional theoretical biology*.… Can a review provide new knowledge? A review can constitute a comprehensive summary of the data in the field — this type of writing educates but does not directly generate new knowledge. *But a 'conceptual' review, on the other hand, can generate knowledge by revealing 'cryptic' data and testing hypotheses by published experiments*.… Conceptual biology should be recognized and criteria established for its publications — new, testable conclusions, supported by published data. In *[psycho]*biological systems, everything is interconnected, and ostensibly unrelated fields are related — the separation of biology into different disciplines is artificial. Conceptual research *[in psychotherapy]* can encompass many fields without limitation. *In comparison with labour-based research, conceptual research is more cost-effective; indeed, verification of a hypothesis using existing data does not limit research to scientists in well-resourced fields or countries. Hypothesis-driven, experimental research will continue to be a corner stone of biology*, but it should strike up a partnership with the essential components of theoretical and conceptual research. (p. 373, italics added)

As can be seen in Fig. 16.1, *in silico* conceptual research proceeds through four recursive stages to uncover new associations that may never have been considered by the original laboratory researchers who first published their data in fields of biology, bioinformatics, chronobiology, genomics, neuroscience, etc. apparently unrelated to the cognitive-behavioral processes of psychotherapy and the creative creative healing experiences of complementary medicine. Most recently, Segal et al. (2007) described a new non-invasive technology for recognizing and decoding gene expression in X-rays of cancer that will greatly expand the possibilities of the visualization stage (fMRI) illustrated in Fig. 16.1.

> Paralleling the diversity of genetic and protein activities, pathologic human tissues also exhibit diverse radiographic features. Here we show that dynamic imaging traits in non-invasive computed tomography (CT) systematically correlate with the global gene expression programs of primary human liver cancer. Combinations of twenty-eight imaging traits can reconstruct 78% of the global gene expression profiles, revealing cell proliferation, liver synthetic function, and patient prognosis. Thus, genomic activity of human liver cancers can be decoded by noninvasive imaging, thereby enabling noninvasive, serial and frequent molecular profiling for personalized medicine. (p. 675)

Figure 16.1 illustrates a neuroscientific perspective on the transformations of consciousness, creativity, imagination, and healing in psychotherapy, complementary medicine, and rehabilitation as a circular biofeedback flow of information between mind and gene. We will now illustrate *in silico* conceptual research with an *ad hoc* example that brings together previously unrelated research from human chronobiology, cognition, behavior, physiology, psychosocial genomics.

16.2 Open Question #2: Psychosocial Genomics: What are the Research Possibilities of Matching Profiles of Gene Expression with Profiles of Psychobiological Behavior in Circadian and Ultradian Time?

Psychosocial genomics has been described as an interdisciplinary field integrating circadian and ultradian profiles gene expression with their associated profiles of behavioral and psychological experience (Rossi, 2002a, 2004a). The focal issue of psychosocial genomics is to create new models of how profiles of gene expression, brain plasticity, and mind-body relationships are interrelated as a complex adaptive system of human experiencing, behavior, and consciousness. Psychosocial genomics has been applied to a wide range of issues ranging from stress, psychosomatics, psycho-immunology, and psycho-endocrinology to the deep psychobiology of creativity (Rossi, 2002b), optimal performance (Rossi, 2002c, d), slow wave sleep and REM dreaming (Rossi, 2002b), art, ritual, cultural, and spiritual experience (Rossi, 2003, 2005; Rossi et al., 2006; Sanders and Mann, 1955).

Figure 16.2 illustrates an approach to *in silico* research in psychosocial genomics by integrating data from the Allen Brain Atlas of Gene Expression with the psychosocial level. Figure 16.2 was assembled by juxtaposing chronobiological relationships between circadian and ultradian profiles of gene expression with profiles of behavior at the cognitive-behavioral level and the physiological level of core body temperature (Rossi and Lippincott, 1992; Rossi, 2004b, 2007). These profiles were assembled as an *ad hoc* juxtaposing of Aldrich and Bernstein's (1987) circadian profile of hypnotic susceptibility (the cognitive-behavioral level), and a typical circadian profile of core body temperature in humans with the circadian profile of the *Thra* gene (the genomic level) in tissues of the heart and liver of the murine rodent (Storch et al., 2002).

The top cognitive-behavioral profile of Fig. 16.2 illustrates the hourly distribution of hypnotic susceptibility scores for Aldrich and Bernstein's college age subjects. We note that this cognitive-behavioral *distribution is bimodal, with peaks at 12:00 noon and 4:00–6:00 p.m.* and a local minimum at 2:00 p.m. Aldrich and Bernstein hypothesize their results provide preliminary evidence that hypnotizability may be related to the circadian rhythm of body temperature at the physiological level. As may be seen, the circadian profile of core body temperature in Fig. 16.2B is also bimodal and closely approximates the circadian profile of hypnotic susceptibility in Fig. 16.2A.

Figure 16.2C illustrates the circadian expression profile of the *Thra* gene, which is also bimodal and resembles the circadian profiles of hypnotic susceptibility and body temperature. The *Thra* gene, coding for the thyroid hormone receptor α, is itself induced by the thyroid hormones T3 and T4, which are fundamental in regulating the physiological work of metabolism and body temperature (Storch et al., 2002). Figure 16.2D illustrates the circadian expression profile of the clock gene *Period* (*Per 1*), which is associated with many daytime activities in humans, and resembles the circadian profiles of hypnotic susceptibility and body temperature

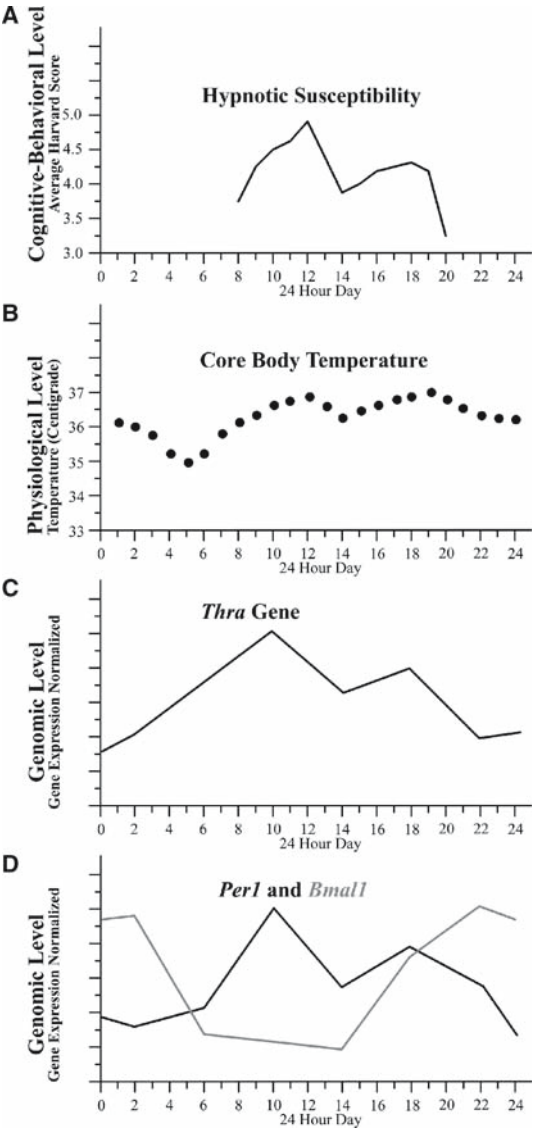

Fig. 16.2 Matching circadian profiles on the cognitive-behavioral, physiological, and genomic levels. This is an *ad hoc* illustration of the psychosocial genomic relationships between the cognitive-behavioral level of hypnosis in (**A**), the physiological level of core body temperature in (**B**), and expression of the *Thra* gene in (**C**) associated with rate of metabolism and body temperature. Figure 16.2**D** illustrates how the circadian profile of the *Per1* gene, typical for the awake state, is similar to the *Thra* gene in (**C**) having a peak of expression about 90–120 min before the peak of hypnotic susceptibility and core body temperature around noon. By contrast notice how the circadian profile of the *Bmal1* gene in (**D**), which is a marker for the sleep state, is in *antiphase* (the opposite of) the awake profiles of *Per1* and *Thra* gene expression associated with peaks of core body temperature and hypnotic susceptibility (Rossi, 2004b)

even more closely than the *Thra* gene. Notice how the circadian profiles of the *Per1* and *Thra* gene are similar in having a peak of expression about 90–120 min *before* the peaks of core body temperature and hypnotic susceptibility around noon. This is consistent with the fact that the 90–120 min ultradian Basic Rest-Activity Cycle (Rossi, 2002a) is typical for many genes to be expressed via gene transcription and translation into the proteins that ultimately generate their physiological and cognitive-behavioral profiles of circadian and ultradian expression (Rossi, 2002b).

Figure 16.1D illustrates the circadian profile of the *Bmal1* gene associated with the sleep state (*the opposite of the Per1* and *Thra* gene profiles associated with being awake). Storch et al. (2002) research on the circadian modulation of gene expression related to body temperature, psychosocial stress (the glucocorticoids), and the immune system (tumor necrosis factor alpha) are of great interest for a psychobiologically oriented approach to therapeutic hypnosis and psychoneuroimmunology at the genomic level. Note the striking similarity of their description of the bimodal circadian profile of gene expression with the bimodal distribution of hypnotic susceptibility scores reported above by Aldrich and Bernstein.

> Many mammalian peripheral tissues have circadian clocks; endogenous oscillators that generate transcriptional rhythms thought to be important for the daily timing of physiological processes. (p. 78) …The *distribution of phases is essentially bimodal, with most genes showing peak expression between circadian time 6 h and 14 h, and a smaller group peaking in phase at about circadian time 20 h*. (p. 81)

Innovative researchers investigating circadian and ultradian profiles of gene expression in the brain, heart, liver, and immune system such as Storch et al. (2002) and others (Panda et al., 2002a,b; Ueda et al., 2002; Rosbash and Takahashi, 2002; Schibler, 2008, this volume), however, do not discuss the implications of their findings for the cognitive-behavioral level of therapeutic hypnosis. Therefore the *ad hoc* assemblage of matched bi-modal circadian profiles of Fig. 16.2 is consistent with *but certainly do not yet prove* that there are causal and reciprocal relationships in the complex interactions between the cognitive-behavioral level of hypnotic susceptibility, physiology, and gene expression. Such proof would require much innovative and integrative psychobiological research to operationalize our next open question (Unterweger et al., 1992).

16.3 Open Question #3: To What Extent Do Top-Down Psychological Processes Modulate Chronobiological Profiles of Gene Expression During Sleeping, Dreaming, and Waking?

Figure 16.3 is a phase histogram, which illustrates the global circadian bi-modal profile of gene expression in the heart and liver, suggests how psychosocial data can be adopted for exploring associations between profiles gene expression, psychophysiology, and complex cognitive-behavioral processes such as therapeutic hypnosis. Panda et al. (2002b) have stated, “The circadian control of transcription

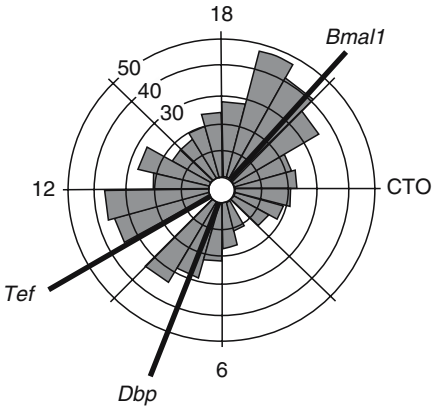

Fig. 16.3 A phase histogram of circadian gene expression in mouse heart and liver. *Bmal1* is a gene with a known robust circadian expression during sleep while the *Dbp* and *Tef* genes serve as phase markers associated with being awake. This circular histogram resembles a circadian 24 h clock face but with CT0 (Circadian Time Zero) on the right representing awakening (or the standardized initial point of data collection such as when movement and physical activity occurs). The nested numbers from the periphery toward the center (50, 40, 30) are the number of genes expressed in each circadian phase of the histogram during this particular experiment (With permission from Storch et al., 2002)

in higher organisms is integrated with the spatial control of *gene expression to target rate-limiting steps in major pathways in their relevant organs, resulting in a systems-level temporal orchestration of behavior and physiology for optimal adaptation of the organism to its environment*" (p. 317, italics added).

Global circadian profiles of gene expression such as Fig. 16.3 may enable us to get a precise answer to a century of controversy regarding the range and limitations of psychological processes and states in modulating the neuro-dynamics of the brain at the molecular-genomic level. Are the circadian and ultradian profiles of gene expression during therapeutic hypnosis, for example, more closely associated with sleep (as proposed by Pavlov, 1927) or the awake state as maintained by Hull (1933/1968)? This question could be answered on the genomic level by investigating the implications of research by Ueda et al. (2002), which they summarize, "Here we demonstrate the role of the Rev-ErbA/ROR response element in gene expression during circadian night, which is in phase with *Bmal1* [during sleep, which Pavlov would predict as associated with hypnosis], and in anti-phase to *Per2* oscillations [while awake, which Hull would predict as associated with hypnosis]" (p. 534).

What is now needed is a more direct assessment of the circadian correlates of therapeutic hypnosis (Rossi, 2002a, 2004a) correlated with core body temperature and profiles of gene expression in high hypnotic susceptible subjects during sleep proposed by Rossi (2004b) somewhat as follows.

> When body temperature is at its lowest point during sleep we could induce hypnosis without awakening the subject (*sleep induced hypnosis*) and keep them occupied with

> personally relevant inner work during hypnosis for an ultradian period of 90–120 minutes. If Pavlov is correct (hypnosis is like sleep) their core body temperature should remain low while their "Rev-ErbA/ROR response element in gene expression" and *Bmal1* gene expression remains at a peak illustrated in Fig. 16.2D (indicating that the circadian night profile of gene expression prevails during sleep and hypnosis). If, on the other hand, Hull is correct we would expect the reverse: core body temperature should rise during the hypnosis and hypnotically induced inner work while subjects were sleeping; on the genomic level their Rev-ErbA/ROR response element and *Bmal1* gene expression should go down in anti-phase with their *per1* gene expression should go up toward a peak as is characteristic of the awake state. Such research would be an important step in answering on the genomic level an issue first raised by the author 20 years ago regarding the degree to which therapeutic hypnosis may *modulate*, *entrain* or *shift* the *phase response curves* (Johnson, 1999) of circadian and ultradian rhythms during health, stress, and illness. (Rossi, 2002a)

> Extending this type of thought experiment even further, it may be possible to differentiate between waking consciousness and therapeutic hypnosis on the level of gene expression. If a difference is found, for example, between the profiles of gene expression in *sleep induced hypnosis* versus a control group (where subjects are simply awakened from their sleep, for example, and kept awake for a similar 90–120 minute ultradian period), these *circadian difference gene expression profiles* may be useful in distinguishing between gene expression during therapeutic hypnosis, normal waking consciousness, and the spectrum of consciousness in creative states and meditation (Wilber, 1993), and psychotherapy in general. Such distinctions would enable us to determine precisely which profiles of gene expression could be modulated by the many schools of psychotherapy ranging from the cognitive-behavioral and psychoanalysis to therapeutic hypnosis. (pp. 19–20)

Such highly innovative and pioneering research would go a long way to determining the quantitative parameters reifying how top-down (Mehta, 2007) processes modulate genomic processes at the molecular level. This top-down approach would be consistent with neuroscience research over the past decade, which has documented the neuro-anatomical processes and functions of our normally varying profiles of gene expression during circadian and ultradian chronobiological rhythms. We will now review the possible significance of one of the most prominent of these neuro-anatomical processes, which has been described as a dialogue between the neocortex, the hippocampus and other sub-cortical areas during off-line states such as slow wave sleep, REM dream sleep, and the "ultradian healing response" during resting states of normal waking consciousness in daily life (Rossi and Nimmons, 1991; Rossi, 2002a, 2004a; Stickgold et al., 2007).

16.4 Open Question #4: Do the Neocortex-Hippocampus Dialogues Function as Cartesian Bridge Between Mind, Gene, Brain, and Body?

Buzsáki's (1996) early description of a dialogue between the neocortex and the hippocampus set the stage for a new research paradigm investigating the functional dynamics of brain anatomy that has attracted an increasing number of

investigators over the past decade (Drosopoulos et al., 2007; Hahn et al., 2007) with these words.

> In gross anatomical terms, the hippocampal archicortex can be conceived as an "appendage" of the large neocortex. In contrast to neocortical areas, the main output targets of the hippocampus are the same as its main inputs (i.e., the entorhinal cortex). *Highly processed information about the external world (the content) reaches the hippocampus via the entorhinal cortex, whereas information about the "internal world" (the context) is conveyed by the sub-cortical inputs. … From its strategic anatomical position and input-output connections, it may be suggested that the main function of the hippocampal formation is to modify its inputs by feeding back a processed "re-afferent copy" to the neocortex. I hypothesize that neocortico-hippocampal transfer of information and the modification process in neocortical circuitries by the hippocampal output take place in a temporally discontinuous manner and might be delayed by minutes, hours, or days*. Acquisition of information may happen very fast during the activated state of the hippocampus associated with theta/gamma oscillations. *Intra-hippocampal consolidation and the hippocampal-neocortical transfer of the stored representations, on the other hand, is protracted and carried by discrete quanta of cooperative neuronal bursts during slow wave sleep*. (p. 81, Italics added here)

Recently Ji and Wilson (2007) and others (Káli and Dayan, 2004) have confirmed that this bi-directional interaction between the hippocampus and the neocortex is necessary for memory consolidation. These researchers believe this dialogue is initiated by the neocortex because its activity occurs sooner than its synchronized counterparts in the hippocampus. *It appears as if the neocortex is querying the hippocampus to replay its most recent raw sensory-perceptual data and memories. This dialogue is not a simple transfer of memory, however, but represents a more sophisticated processing of data whereby the neocortex selects novel information from the hippocampus*. Researchers suggest that from a top-down perspective, the neocortex is trying to make sense of what is going on in the hippocampus and to build models of the world to understand how and why things happen. These top-down models presumably generate new expectations about the world, which direct cognition, creative planning and adaptive behavior in *the evolutionary memory-prediction framework of intelligence* (Hawkins and Blakeslee, 2004, p. 177; Rossi et al., 2008, in press). We have proposed these top-down neuro-anatomical models as an emerging framework for the deep psychobiological foundation of virtually all schools of psychotherapy and rehabilitation (Rossi, 2007; Rossi et al., 2006, 2007).

16.5 Open Question #5: Is the Offline Replay of Circadian and Ultradian Rhythms the Essence of the Creative Experience in Art, Beauty and Truth?

Figure 16.4 is a profile of the human brain with a focus on the hippocampus, which only makes a temporary recording of new memory, learning or behavior, however. Later, during "offline periods" of sleep, dreaming, and rest when the conscious mind is not actively engaged in dealing with outer realities, the neocortex and hip-

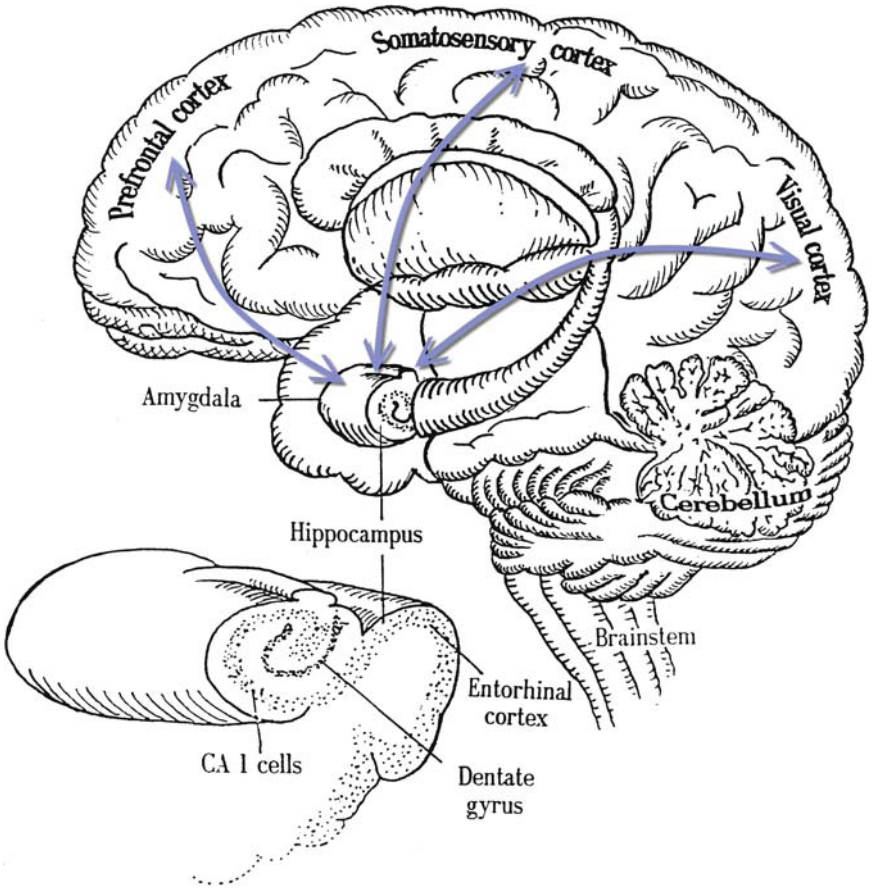

Fig. 16.4 The neocortex and hippocampus dialogues. During "offline" periods of slow wave sleep, dreaming, and rest when the conscious mind is not actively engaged in coping with outer realities, the neocortex and hippocampus (and other sub-cortical brain structures) engage in dialogues to update, replay, and consolidate the new memory and learning in the neocortex where the 'local-global computations' of consciousness are thought to take place (Pereira et al., 2007)

pocampus engage in a neural dialogues to update, replay and consolidate the new memory in more permanent storage locations throughout the neocortex. *These mind-brain-gene dialogues activate and creatively replay the 'local – global computations' of the neocortex (Buzsáki, 2006), which are now believed to be the neural correlates of consciousness long sought by the late Francis Crick.*

Lisman and Morris (2001) describe how this offline dialogue activates and replays novel and significant life experience between the cortex and hippocampus of the brain as follows.

> … newly acquired sensory information is funneled through the cortex to the hippocampus. Surprisingly, only the hippocampus actually learns at this time — it is said to be online. *Later, when the hippocampus is offline (probably during sleep), it replays stored informa-*

> *tion, transmitting it to the cortex. The cortex is considered to be a slow learner, capable of lasting memory storage only as a result of this repeated replaying of information by the hippocampus*. In some views, the hippocampus is only a temporary memory store — once memory traces become stabilized in the cortex, memories can be accessed even if the hippocampus is removed. *There is now direct evidence that some form of hippocampal replay occurs.… These results support the idea that the hippocampus is the fast online learner that "teaches" the slower cortex offline*. (pp. 248–249, Italics added)

We have proposed that these entirely natural psychobiological "dialogues" between our neocortex and hippocampus is the essential process that we attempt to facilitate in our emerging mind-gene model of creativity, psychotherapy and rehabilitation. From this psychological perspective, therapeutic suggestions, interpretations, metaphors, cognitive behavioral interventions etc. could be more aptly described as *"implicit processing heuristics,"* which facilitate the natural offline dialogues between our hippocampus and the cortex. *We propose that the conscious and explicit dialogues between therapist and client in psychotherapy are efficacious to the extent that they facilitate the appropriate offline, unconscious, and implicit dialogues between the neocortex, the hippocampus and other subcortical structures that daily and hourly update consciousness by turning on activity-dependent gene expression and brain plasticity*. Permissive suggestions, which we now call "Implicit processing heuristics" in the therapist/client dialogue, are creative cues and hints that we use to facilitate the offline cortex/hippocampus dialogues that evokes *activity-dependent* gene expression and brain plasticity for adaptive behavior change (Ribeiro et al., 2008; Rossi, 2002a, 2004a, 2007; Toni et al., 2007, 2008).

If people have problems it usually means they are stuck somewhere in stage two of the four stage creative process (Rossi, 2007; Wallas, 1926) as illustrated in Fig. 16.5 in one area or another of their lives – this is when most people tend to fall into a crisis and come to psychotherapy looking for help. The wise therapist, however, knows that the "presenting problem" is usually only a ripple on the surface of the deeper waters of self-care and creative life management. Our new chronobiological model of the creative process illustrated in Fig. 16.5 implies that every creative individual needs to learn how to breakout of previously learned limitations on all levels from mind to gene expression and brain plasticity (Toni et al., 2007). Facilitating this very general paradigm of the creative process is called, "The Breakout Heuristic" in our growth-oriented model of psychotherapy (Rossi, 2007).

Of all the creative arts, music and appears to be the one most dependent on rhythm and timing. This suggests we might expect to find evidences of ultradian and circadian rhythms in music as illustrated in Fig. 16.6. Figure 16.6 illustrates how the creative experience of the *sonata form*, a four-stage paradigm of musical composition widely in classical music, has essentially the same profile as chronobiological profile of the four-stage creative process in Fig. 16.5 (Kamien, 2006). The term "*sonata form*" refers to the first movement of a symphony. The opening movement of a classical symphony, for example, is usually in sonata form (often called *sonata-allegro*). The sonata form has three main sections (the *exposition*, *development*, and *recapitulation*) that are often followed by the *coda*, a brief concluding section.

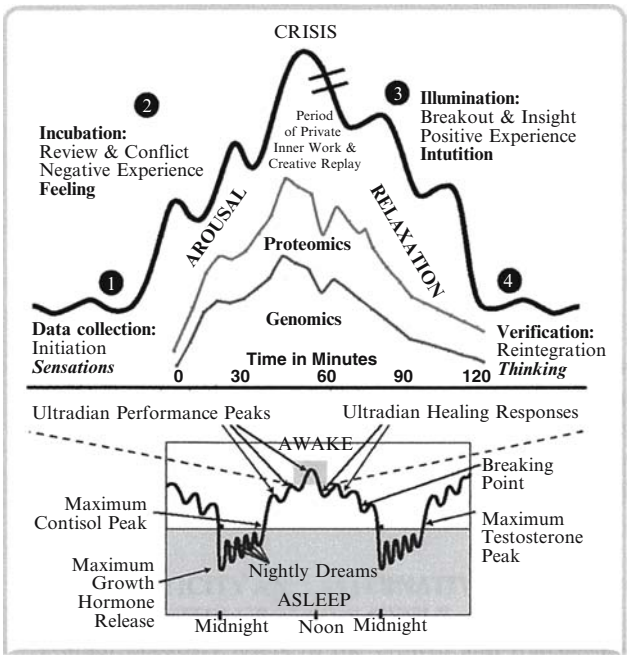

Fig. 16.5 The chronobiology of the four stage creative cycle. The ultradian profile (90–120 min) of the classical four-stage creative process as it is typically experienced on the subjective psychological level is illustrated in the top most portion of the upper curve. The proteomics (protein) profile in middle curve depicts the energy landscape for protein folding within neurons of the brain into the correct structures needed for brain plasticity (Ealch et al., 2008; Cheung et al., 2004). This proteomic profile arises from the functional concordance of co-expressed genes illustrated by the genomics profile below it (Adapted from Levsky et al., 2002). This genomics curve represents the actual gene expression profiles of the immediate-early gene *c-fos* and 10 other genes (alleles) over the typical Basic Rest-Activity (BRAC) period of 90–120 min. The lower diagram illustrates how these ultradian dynamics of the qualia of consciousness are typically experienced as Kleitman's 90–120 min Basic Rest-Activity Cycle within the normal circadian cycle of waking and sleeping (Rossi, 2002a, 2004a; Rossi and Nimmons, 1991)

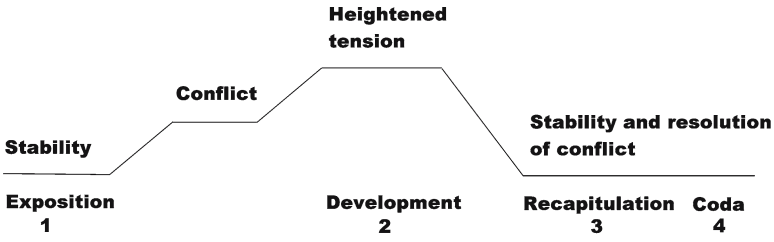

Fig. 16.6 The Sonata form of classical music. The sonata form of classical music is usually profiled in four movements, which we propose as corresponding to the four stages of the creative process in Fig. 16.5. Recall how the classical octaves of music theory are also made up of two tetrads (four notes in a tetrad). Further research may establish how rudimentary forms of these four stages of the classical creative process are also evident in the quatrains of poetry, lyrics, and song as well as alchemy and psychology (Jung, 1953, 1927)

The sonata form illustrates how composers of the classical period (1750–1820) such as Haydn, Mozart, and Beethoven used the language of music to tell "stories" that resonated with the human condition for over 200 years. In a book on music appreciation, Kamien (2006), states: *"The amazing durability and vitality of sonata form result from its capacity for drama. The form moves from a stable situation toward conflict (in the exposition), to heightened tension (in the development), and then back to stability and resolution of the conflict."* We now propose that the durability and vitality of the sonata form also comes from its integration of multilevels of human experiencing from mind to the molecular-genomic. In the following Kamien's descriptions of the four stages of the sonata form are noted in italics along with our descriptions of their correspondences to the four stages of the creative process in regular font.

1. *"The **Exposition** sets up a strong conflict between the tonic key and the new key. It begins with the first theme in the tonic, or home, key. There follows a bridge, or transition, leading to the second theme, in a new key."* This initial stage of the sonata form corresponds to stage one of the creative process when therapist and patient seek to identify the problem (first theme) and the life changes (second theme) that are at the source of patient's conflicts of stage two.
2. *"The **Development** is often the most dramatic section of the movement. The listener may be kept off balance as the music moves restlessly through several different keys. Through these rapid modulations, the harmonic tension is heightened. In this section, themes are developed, or treated in new ways. They are broken into fragments, or motives, which are short musical ideas developed within the composition. A motive may take on different and unexpected emotional meanings."* This second part of the sonata form corresponds to stage two, the incubation stage of the creative process, with its characteristic conflicts, negative emotions, and symptoms.
3. *"The beginning of the **Recapitulation** brings resolution, as we again hear the first theme in the tonic key.… Earlier in the exposition, there was a strong contrast between the first theme in the home key and the second theme and closing section in a new key; that tension is resolved in the recapitulation.… "* This third section of the sonata form obviously corresponds to stage three of the creative process when there is a resolution of the conflict, problems, and symptoms of stage two.
4. *"An even more powerful feeling is attained by following the recapitulation with yet another section. The coda rounds off a movement by repeating themes or developing them further. It always ends in the tonic [home] key."* Note how this fourth and final part of the sonata form corresponds to stage four of the creative process in illustrated in Fig. 16.5 (Adapted with quotations from Kamien (2006, pp. 163–164) in italics).

Note how well the four stages of the sonata form described in Fig. 16.6 appear to correspond to the four stages of the creative process in Fig. 16.5. This leads us to propose that Fig. 16.6 is a striking illustration of how the creative arts (music, dance, drama, myth, poetry, song, stories, etc.) may be understood as performance

modalities for the therapeutic replay, reconstruction, and reframing of negative human experiences into positive perspectives that many cultures have called "healing, therapeutic, rehabilitation and wisdom." Indeed, many of the classical composers such as Beethoven and Schubert were know to use their musical improvisations for healing that "said everything and gave solace to the sufferer in his own language" (Solomon, 2003, p. 229). This leads us to propose that *numinous experiences* (such as *fascination*, *mysteriousness*, and *tremendousness*, Otto, 1923/1950) of art, beauty, and truth could initiate the *activity* of positive healing experiences when they generate the top-down *activity-dependent* gene expression, brain plasticity, and their natural psychophysiological consequences in the psychoneuroimmunology, psycho-endocrinology, etc. (Rossi, 2002a, 2004a, b, 2005, 2008).

16.6 Open Question #6: What Is the Ultimate Molecular-Genomic Source of Kleitman's Ultradian 90–120 min Basic Rest-Activity Cycle?

A review of early conceptions of the relationships between ultradian rhythms, the periodicity of the endocrine system, and psychosomatic problems as fundamental for understanding the implications of Kleitman's 90–120 min Basic-Rest-Activity Cycle (BRAC) for general health and optimal performance was stated as follows (Rossi, 1986/1993).

> One of the most interesting recent theories about the genesis of psychosomatic problems is that they *result from the behavioral disruptions of the ultradian rhythms that modulate both autonomic and endocrine system functioning*. Orr, Hoffman, and Hegge (1974), for example, reported that most humans manifest a stable ultradian rhythm when under quiet conditions. When their subjects were overstressed with extended performance tasks (e.g. monitoring complex panel meters), however, their ultradian rhythms underwent major disruptions in amplitude and patterning. (p. 134)

This conception was generalized into a therapeutic approach to psychosomatic problems by teaching people how to recognize they had a behavioral choice between experiencing an "*Ultradian Healing Response*" by taking an appropriate healing 20 min rest break every 90–120 min or so throughout their busy day, versus their habitual ignoring of their natural mind-body signals for rest that generated a "*Ultradian Stress Response*," which resulted in their psychosomatic symptoms (Rossi and Nimmons, 1991). This therapeutic approach is supported by more recent neuroscience research on new methods of measuring Kleitman's BRAC (Shono et al., 2001) and the recognition of the "protective effect of ultradian rhythms" (Duchniewska and Kokoszka, 2003).

While great progress has been made recently in elucidating the molecular-genomics of the circadian clock (Grimaldi and Sassone-Corsi, 2007; Schibler, 2008, this volume), the mechanisms of Kleitman's ultradian 90–120 min Basic Rest-Activity Cycle remains poorly understood at this level. Lin et al. (2007), for example, have identified the transcriptional coactivator PGC-1 as a key component

of the circadian oscillator that integrates the mammalian clock and energy metabolism as follows.

> We have identified PGC-1α, a major metabolic regulator, as a critical component of the mammalian clock. PGC-1α stimulates the expression of *Bmal1* through coactivating the ROR family of orphan nuclear receptors and is essential for normal circadian rhythms. *Because PGC-1α expression is highly responsive to nutritional signals and potentially light, our findings support a mechanism through which energy metabolism and circadian clock can be directly coupled at the transcriptional level. PGC-1$^{\alpha}$* null mice are resistant to diet-induced obesity and are more insulin-sensitive, whereas *Clock* mutant mice develop obesity. These differences are probably due to the fact that *PGC-1$^{\alpha}$* null mice are hyperactive and have a higher metabolic rate in the absence of increased food intake. Our findings raise an intriguing possibility that the expression and/or activity of PGC-1α itself may be regulated by components of the clock oscillator. *Because feeding and locomotor activity are regulated by circadian clocks, it is possible that rhythmic PGC-1α expression is controlled by these physiological and behavioural rhythms*. Alternatively, PGC-1α is associated with the SirT1 histone deacetylase complex and may directly sense the metabolic state of the cell, in a similar way to the regulation of the clock homologue NPAS2 by redox status. *Disruption of circadian rhythms has been implicated in the pathogenesis of metabolic disorders. Our studies have uncovered a potential molecular target that could simultaneously modulate circadian clocks and energy metabolism*. (p. 480, italics added here)

The open question now is whether transcriptional coactivator PGC-1 and/or other transcription factors functionally related to it are also key components of Kleitman's ultradian 90–120 min Basic Rest-Activity Cycle. More recently McClung et al. (Talan, 2007) reported that *Clock* mutant mice manifest many of the same symptoms as humans diagnosed with mania and bipolar behavior. Their work implies that the clock gene is a major source of circadian behavior and mood regulation in humans. The *Clock* mutation is now known to disrupt dopamine neurons, which play a important role in mood, activity level, motivation, and pleasure. Continuing research at the molecular-genomic level of transcription factors that activate *Clock* gene expression and related brain plasticity would certainly go a long way toward integrating the deep psychobiology of broad classes of apparently unrelated phenotypic behaviors characteristic of the wave nature of human consciousness and being in creative and motivating experiences of art, beauty and truth (Rossi, 2005, 2007; Rossi & Kleitman, 1992).

16.7 Open Question #7: Will it be Possible to Develop a "Mind-Gene Biofeedback Device" Whereby Voluntary Conscious Mental Activity Could Modulate Activity-Dependent Gene Expression and Brain Plasticity for Mind-Body Healing?

At what levels would a mind-gene biofeedback device or psychological process operate? That is, how would a top down device or psychological process focus consciousness and attention to modulate the dynamics of activity-dependent gene expression? Current concepts and research in epigenetics (Bird, 2007; Feinberg,

2007; Fraser and Blickmore, 2007) suggests that transcription factors are a bridge between environmental stimuli, mental activity, and activity-dependent gene expression, brain plasticity, and a host of other apparently unrelated psychobiological fields of activity such as psychoneuroimmunology, psychoendocrinology, stress, optimal states of creativity and flow in everyday life as well as psychotherapy, rehabilitation, and medicine in general (Rossi, 2008; Rossi and Cheek, 1988).

A brief review of how a mind-gene biofeedback device could be put together has been proposed by Rossi (2004a) and updated here as follows.

> Will it be possible to develop a *mind-gene biofeedback device* in the future that would allow us to modulate activity-dependent gene expression and brain plasticity just as we now use inexpensive biofeedback devices to modulate muscle relaxation? This would be the ultimate kind of mind-body biofeedback that theoretically could facilitate to any type of psychophysiological healing at the molecular-genomic level.
>
> To make a mind-gene biofeedback device we need a *mind-gene transducer*. That is, we need to invent a transducer or "transformer" that converts a highly stimulating and activating subjective psychological experience (novel and numinous *activity* on the cognitive-behavioral level) into a neocortical – sub cortical dialogue (e.g. the neocortical – hippocampus dialogues reviewed above) that would activate series of molecular signals and transcription factors that would turn on *activity-dependent* gene expression and *activity-dependent* brain plasticity. Recent research in nano-technology suggests how this may be possible. (Hahm and Lieber, 2004)
> "Nano" means billionths of a meter, or a hundred-millionths of an inch – much smaller than the usual meaning of small. Individual atoms are just a few nanometers in diameter. This is the scale at which atoms are assembled to form the molecules that create the basic building blocks of life such as DNA, genes, and proteins. With but few exceptions every cell in the body contains the entire genetic code consisting of about 3 billion "base pairs" of nucleotides for making the body's 10 trillion cells. Since these cells replace themselves every few years, the human body makes new DNA at the estimated rate of 10,000 miles an hour! Nature, of course, makes DNA at an implicit or unconscious level. Our proposal for a mind-gene biofeedback machine would be a way of introducing consciousness more directly into the process of modulating DNA production, gene expression, brain plasticity, and mind-body healing. This may be possible via the new "nanolab chips" currently under development.
> Researchers at the California Institute of Technology, UCLA, IBM, and the Institute for Systems Biology in Seattle are creating nanolab chips that greatly improve the speed and efficiency of our current DNA microarray (gene chip) technology. Nanolab chips will be able to analyze what is happening within individual cells in *a few seconds or minutes* what it takes current microarray technology hours to accomplish with much larger tissue samples. These nanolab chips contain nano-mechanical sensors to detect protein and gene interactions (i.e. gene transcription) that could become part of a mind-gene transducer that would be the essence of our proposed mind-gene biofeedback device. The heart of these nano-mechanical mind-gene transducers could be a nano-wire sensor that produces an electric signal when it binds to a gene and/or protein such as a transcription factor and a wide range of other signaling molecules (Hahm and Lieber, 2004). This electric signal can then be amplified to produce an image on a computer screen that would enable *human subjects to use their consciousness to detect when they are in modulating activity-dependent gene expression and brain plasticity*. This is the type of mind-gene transducer that would make the ancient alchemical dream of mind-body communication and healing possible in real time with a practical mind-gene biofeedback device (de Waele et al., 2007; van Hulst, 2007). It already has been proposed that such direct detection and imaging of gene expression could enable researchers use a single drop of blood to screen patients for all the known human genetic disorders (Goho, 2004)." (pp. 304–305)

16.8 Summary and Conclusions

Many fundamental issues must be resolved to facilitate the emerging sciences, technologies, and therapies in response to the open questions of this chapter. We need intensive research in the new sciences of epigenetics and psychosocial genomics to explore the range and limitations of how we can utilize the top-down permissive suggestions (i.e. "implicit processing heuristics") to modulate the cascades of molecular signals between mind and body ranging from the receptors on the surfaces of the cells to the nuclear transcription factors that turn on activity-dependent gene expression and brain plasticity. Conventional image amplifying devices are limited in their resolving power by the diffraction of light with traditional lenses and mirrors. Recent discoveries in nano photonic technology, however, have broken through the diffraction limit of conventional optics to image the molecular-genomic level. This new imaging power down to the molecular-genomic level is what would make it possible to create an in vivo gene sensor and mind-gene biofeedback medical and psychological device for facilitating human performance and healing. We need to energetically monitor websites of neuroscience, chronobiology, epigenetics, functional genomics, nano-technology, etc. to pick up the conceptual breakthroughs, which will implement our emerging sciences, technologies, and therapies to facilitate human consciousness and its potentials in a manner that will be worthy of a Nobel Prize in the future.

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