

Temporal organization of the brain: Neurocognitive mechanisms and clinical implications[☆]

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Abstract

The synchrony between the individual brain and its environment is maintained by a system of internal clocks that together reflect the temporal organization of the organism. Extending the theoretical work of Edelman and others, the temporal organization of the brain is posited as functioning through “re-entry” and “temporal tagging” and binds the wide range of possible times to a unified cognitive experience which is held in unison with the outside world. Dysfunction in this system is reflected in the temporal discord seen in cases of aging, sleep disorder, jet-lag, and shift-work, as well as in mental disorders and drug-induced changes in consciousness. The extent to which neuroendocrine structures contribute to the neurocognitive mechanisms which underlie consciousness has so far not been explored. Therefore, neuroendocrine mechanisms contributing to the temporal organization of the brain are reviewed. It is concluded that time—and its neuroendocrine correlate melatonin—is a binding principle for organizing conscious experience.

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“To everything there is a season and a time to every purpose under heaven.”

The Holy Bible, Book of Ecclesiastes, Chapter III: v.1-8

“Every reference-body (co-ordinate system) has its own particular time; unless we are told the reference-body to which the statement of time refers, there is no meaning in a statement of the time of an event.”

Einstein (1961, p.31)

1. Introduction

The role of time in consciousness has been studied since the ancients (see, for example, Plato, 2001). Of recent interest in this context is the suggestion that cognition is intrinsically temporal (Shanon, 2001). Consistent with this, Penrose (1994) has also proposed that “it is only the phenomenon of consciousness that

requires us to think in terms of a ‘flowing’ time at all” (p. 384). Indeed, the very notion of cause-and-effect, with its assumption that causes always precede effects—which regulates human goal-directed behaviour and the achievement of a previously planned goal—is wholly dependent on the development and coding of temporal orientation (Friedman, 1989). Thus, the thesis of this paper is to review a broad base of evidence which provides a set of putative mechanisms underlying what I call temporal cognition or “temporal consciousness.” While this review is not exhaustive, it follows an integrative cognitive neuroscience approach to the study of temporal information processing (e.g., Pylyshyn, 1979; Rammsayer, 1994).

Recent research suggests that the role of time in human consciousness resides primarily in systems which maintain synchrony between the neurochemistry of the brain and the environments available to the organism. This synchrony, harmony, or “binding” of internal and external environments is maintained for the organism by a system of internal clocks. Together, these synchronizing, binding systems reflect the temporal organization

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of the organism. These internal clocks have both neuronal and endocrine components, which will first be briefly described. This will be followed by a discussion of the implications of neuroendocrine mechanisms for the study of temporal disorganization—in other words, a loss of temporal binding—to be found in aging, in altered states of consciousness, and, more extremely, in mental illness.

2. Neuronal mechanisms of temporal organization

Virtually every physiological system is rhythmic (Glass & Mackey, 1988; Moore-Ede, Sulzman, & Fuller, 1982). For example, breathing, heart rate, blood pressure, muscle tone, activity level, and state of consciousness, are all regulated by internal biological clocks. Partly because of this diversity of needs for timing the functioning of organs throughout the body, the brain itself has been suggested to be a clock. For example, Melges (1989) proposes the dependency of time parameters on the brain, stating: “when the brain is impaired by diffuse chemical or neuronal imbalances, all components of time sense—sequence, rate, and temporal perspective—go awry” (p. 102). Likewise, Fraser (1975) suggests the whole brain is an “organ of time sense” (cited in Melges, 1989, p. 110).

However, there is evidence that different regions of the brain regulate different aspects of temporal organization. For example, the suprachiasmatic nucleus of the hypothalamus (SCN) is thought to tag 24-h cycles. That is, it seems to be an endogenous circadian clock (having an approximately 24-h period) and thereby regulates sleep and wakefulness, even in the absence of environmental fluctuations in light and dark (Moore & Card, 1985). In addition, when the timing of the light/dark cycle is phase-shifted, the sleep–wake cycle is reset or “re-entrained” and neuronal firing in the SCN is a critical participant in this adaptive shift to changed environmental conditions (Arendt et al., 1987; Armstrong, Cassone, Chesworth, Redman, & Short, 1986; Lynch et al., 1978).

While it is thought that the SCN regulates the body’s rhythms in relation to the day–night cycle, other structures seem to track a linear form of temporal information. With respect to the latter, for example, the hippocampus tags information about the past while the frontal cortex tags expectancies for the future. Melges (1989) summarizes the role of brain structures in timing cognitive functioning. Melges (1989) reviews evidence that the disruption of the left hippocampal–limbic–prefrontal network is critical in the irrelevant associations, perseveration, and loss of drive and initiative observed in schizophrenia. Moreover, Barkley (1997) has suggested the fundamental dysfunction in Attention Deficit Hyperactivity Disorder (ADHD) is a temporal pro-

cessing dysfunction that is characterized by an inhibitory deficit in the prefrontal cortex. Consistent with Melges (1989), functions attributed to the frontal lobe such as delayed gratification, comparison of possibilities, selection of present events from among past memories and future expectations, are all disrupted in schizophrenia. Likewise, there is a growing literature suggesting these same temporal dysfunctions appear in children and youth with ADHD (Barkley, 1997; Kerns, McInerney, & Wilde, 2001; West et al., 2000). Immediate memory breaks down and filtering of irrelevant information is disrupted. Under these conditions, according to Melges, “the then would invade the now” (p. 115) and, in the language of the binding problem (see, for example, Edelman & Tononi, 2000), the world would become “temporally unbound.”

Other studies suggest that temporal organization overlaps with attentional processes regulated by transient synaptic assemblies (Crick, 1984), suppression of neural responses (Luck & Beach, 1999), long-range reciprocal connections (Damasio, 1989), and temporal correlations or temporal tagging of features (Alais, Blake, & Lee, 1998; Rickert, Duke, Putzke, Marson, & Graham, 1998), dynamic units, or elements (Mandelblit & Zachar, 1999). For example, cortical neurons have been shown to code visual stimuli in terms of the timing of their presentation (Alais et al., 1998). In addition, differences in recognition memory between early-stage Alzheimer’s patients and non-Alzheimer’s controls appeared only in remembering *when* not in remembering *what* they had seen (Rickert et al., 1998). Moreover, Henson (1998) found that detection or tagging of an immediate repetition is a necessary element in the process of recall of items presented close together but not far apart in time.

The synchronization of diverse, discontinuous, or missing elements into a unitary perceptual experience has been proposed to depend on “re-entry” mediated by reciprocal connections (Wray & Edelman, 1996). However, it may also depend on neural activity in multiple regions occurring simultaneously (Damasio, 1989). This makes sense in terms of Edelman’s simulation studies in which neurons responding to various attributes of the same object were synchronized and neurons responding to different objects were asynchronous (Edelman & Tononi, 2000). They also found synchronization at different time scales, with groups of neurons showing firing bursts on the order of tens of milliseconds and periodically “re-entering” another group of neurons with output at the scale of hundreds of milliseconds (Edelman & Tononi, 2000). Thus, Edelman suggests a “re-entrant” system is capable of fine-tuning temporal differences and the strength and speed of these temporal interactions could participate in the self-perpetuating dynamic process of consciousness. Not only that, “this coherent process is quite stable, being capable of

sustaining itself continuously while changing its precise composition. This stability means that although there is always a large pool of synchronously firing neurons, the neurons actually engaged in this pool change from moment to moment” (Edelman & Tononi, 2000, p. 119).

3. Neuroendocrine mechanisms of temporal organization

Beyond the electrical signalling properties of neurons, the brain incorporates processes regulating both cellular events and events occurring among chemicals in the gap between cells (i.e., the synapse). As such, these can be called neurochemical—even neuroendocrine—mechanisms. Indeed, the brain functions as a large endocrine gland (Reinis & Goldman, 1982) and it is difficult to elicit a clear separation of the brain’s chemical processes from its electrical ones. For example, the brain’s structure and function is neurochemical (including enzymes, membrane lipoproteins and ion channels, microtubules, and neurotransmitters). These have actions affecting thoughts, emotions, and behaviours (e.g., see Reinis & Goldman, 1982).

One set of recent studies describing the role of a neuroendocrine system in consciousness—and in which time plays a key role—has been conducted by Edelman’s group (Edelman & Tononi, 2000; Srinivasan, Russell, Edelman, & Tononi, 1999; Tononi & Edelman, 1998; Wray & Edelman, 1996). The research of Edelman’s group in general supports “the dynamic core hypothesis.” This hypothesis suggests that conscious experience is both integrated (or unified) and at the same time differentiated (or diversified) by reciprocal neural connections throughout the cerebral cortex and between the cortex and the thalamus. These neural pathways are presumed to ensure that changes in local synaptic connections are held in the context of spatiotemporal correlations in more distant areas of the brain. Such context-dependent changes are important in selectional learning, which Edelman and his group have examined in their simulation studies. In these studies, neurotransmitters and hormones play a role in modulating the process of re-entry through a set of “diffusely projecting value systems” which have evolved to carry information about the behavioural state of the organism to neurons and synapses throughout the brain. In addition, these neurochemical “value systems” signal the brain regarding salient and unexpected events like rewards, pain, and novel stimuli. For example, when something happens that might threaten survival or require adaptation, sudden bursts of neural firing occur and neuro-modulators are released over most brain regions. According to this model, “value systems” limit both the events available for selection and the extent of synaptic changes that occur with experience. Edelman and Tononi (2000) give the example of orientation towards a

light source being governed by neurochemical value systems; however, they state that neurochemical value systems may not be sufficient for identifying the object that is the source of reflected light.

Extending Edelman’s proposed model, additional candidates in a “re-entrant” or neural loop system are those in which “re-entrainment” commonly occurs (e.g., Quay, 1970a, 1970b, 1972). This does *not* differ from Edelman’s theory, as he says:

“These systems, whose importance vastly outweighs the proportion of brain space they occupy, include the noradrenergic, serotonergic, cholinergic, dopaminergic, and histaminergic nuclei... These neurons give rise to a vast network of axons that blanket the cortex, hippocampus, basal ganglia, cerebellum, and spinal cord, potentially influencing transmission at billions of synapses over all levels of the central nervous system... Neurons within some of the nuclei of value systems fire in a continuous or tonic manner when an animal is awake and stop firing when the animal falls asleep” (Edelman & Tononi, 2000, p. 89).

Such pathways are neuroendocrine and have the capability of synchronizing, resetting, or stabilizing each other. This process, also called “entrainment,” maintains synchronization with the time at which a regularly repeating phenomenon occurs. For example, most people wake up at a certain time each morning. They go to sleep at a certain time each night. However, when these times are shifted in the case of shift-work or delayed sleep phase insomnia, for instance, the circadian clock adapts. This adaptation involves phase-shifts or “re-entrainment.” That is, the circadian clock is reset to a later point in time than the usual bedtime, which makes it more difficult to get to sleep when desired. To do this, signals concerned with lighting and the onset of sleep activate specific neural networks at a particular time-point and “re-enter” the circadian clock to set it.

An additional example of re-entry is initiated by consciously deciding when to wake up without relying on an alarm clock. There is evidence that many people experience considerable success with this cognitive manipulation (Moline & Monk, 1988; Monk, 1990; Monk & Moline, 1989). From what is known about the brain, this probably involves prefrontal cortical pathways sending signals via the thalamus to the hypothalamus where the clock is reset. There is evidence for pre-programmed neurochemical changes at the time just prior to falling asleep (Golombek, Pevet, & Cardinali, 1996; Skene, Deacon, & Arendt, 1996). Thus, an integrated system comprised of neural and hormonal elements (including prefrontal, thalamic, and hypothalamic activation) may be important in obtaining orientation, identification, and arousal features of consciousness. Indeed, an integrated neurohormonal system is exactly what has been found when systems of biological clocks have been examined.

Many neuromodulators qualify as candidates for participation in the diffuse value systems that limit events available for selection. Such neuromodulators include serotonin and norepinephrine. These are neurotransmitters involved in regulating activities related to species survival such as sleep, eating, drinking, and sexual behaviour. For example, neurons which synthesize serotonin and norepinephrine are located in the brainstem and in the hypothalamus. Some of these are active during wakefulness and inactive during sleep.

Neural firing in the SCN is known to inhibit secretion of the pineal gland hormone melatonin, a sedative neuromodulator thought to play a role in re-entrainment such as occurs in shift-work and jet-lag. Likewise, the SCN and melatonin act reciprocally to time behaviour. While the SCN appears to generate the circadian rhythm in melatonin secretion, the SCN itself is acted upon by melatonin. Evidence for this comes from studies of the absence of the SCN, in which melatonin had no effect on re-entrainment (Cassone, Chesworth, & Armstrong, 1986; Frazer & Brown, 1987; Murakami, Hayafuji, Sasaki, Yamazaki, & Takahashi, 1983) and from more recent studies of melatonin receptors in the SCN (e.g., Piggins, 2002; von Gall, Stehle, & Weaver, 2002).

Thus, it is proposed here that the pathways involved in temporal organization (including the SCN, the pineal, and melatonin) are important parts in the “re-entrant” process responsible for temporal consciousness. Consistent with this proposal, the important role in temporal organization played by brain structures such as the SCN and the pineal gland has been well studied and has been widely acknowledged for 20 years (e.g., Cassone et al., 1986; Frazer & Brown, 1987; Murakami et al., 1983). Clearly, then, there is ample empirical evidence to suggest that the SCN, the pineal gland, and melatonin play an important role in systems synchronizing the periodic re-entry of consciousness coincident with the environmental alteration of day and night. However, the extent to which these neuroendocrine structures contribute to the complex combinations of available neurotransmitter systems which underlie consciousness itself has so far not been explored. Even so, like the question of time, the role of the pineal gland in consciousness and selective attention has been the subject of speculation since the time of the ancients. A discussion of this illustrates further a putative role of neuroendocrine processes underlying temporal consciousness.

4. The pineal and consciousness

Over 2000 years ago, the Egyptian anatomist Herophilos (325–280 B.C.) discovered the pineal organ and believed that it functions as a tap regulating the stream of “pneuma” from the third to the fourth ventricle.

He considered this process, influenced by sensory input, to be the direct cause of the development of knowledge. Some time between 130 and 300 A.D., Galen named the pineal organ “soma konoeides” because of its resemblance of the pine cone but did not agree with the “tap” function of the gland proposed by Herophilos (Kappers, 1979). In the 17th century, René Descartes, the French philosopher-mathematician, became famous for his views on the mind-body problem. Pavlov (1927) rightly dubbed Descartes the father of biopsychology: “Our starting point has been Descartes’ idea of the nervous reflex. This is a genuine scientific conception, since it implies necessity... Thus a stimulus appears to be connected of necessity with a definite response, as cause with effect... If the animal were not in exact correspondence with its environment it would, sooner or later, cease to exist” (Pavlov, 1927, pp. 7–8). The pineal gland, according to Descartes, provides the executive medium for all correspondences between stimulus and response by virtue of it being “the seat of the soul” (e.g., Carter, 1983).

As William James made clear just before the turn of the 20th century, attention oscillates not only between stimuli in the spatial environment but also in time. “When two different stimuli—e.g., a sight and a sound—are given at once or nearly at once, we have difficulty attending to both, and may wrongly judge their interval, or even invert their order. Now, as a result of his experiments on such stimuli, Wundt lays down this law... of discontinuous succession in time, of percepts to which we cannot easily attend at once. Each percept then requires a separate brain-process; and when one brain-process is at its maximum, the other would appear perforce to be in either a waning or a waxing phase” (James, 1891, p. 417). Descartes referred directly to the temporal and lateralized aspects of pineal executive function in his *Passions of the Soul*: “When one wants to arrest his attention to consider that object for a period of time, this will retain the gland, during this time, sloping towards the same side...” (quoted in Carter, 1983, p. 129).

From the time of the ancients, the pineal gland has figured prominently in speculations about the regulation of the critical process of conscious attention. We see in the next section that these philosophical suppositions have a basis in fact.

5. Role of the pineal in sensory attention

Following James’ (1891) commentary in relation to Wundt’s law of discontinuous succession, attentional processes have been studied as perhaps the principle executive function of consciousness—likely contributing significantly to the assumption that human consciousness can attend to only one thought at a time. In ar-

gument against this corollary of Wundt's law, it should be noted that it is apparent from the evidence presented that temporal consciousness is more complicated than a single stream or "flow of consciousness" which allows only one event at a time. Instead, while temporal consciousness may include this linear flow, it also includes the cycle of sleep and wakefulness, each alternating with the other, approximately synchronized with the number of days and nights in the person's life. For example, a person might pay more attention to the need to achieve certain future career goals while ignoring the growing need for sleep, but these two items are present simultaneously and relatively, one losing meaning without the other. Thus, the neural mechanisms (such as those regulated mainly by the hippocampus and basal forebrain) can be seen to underlie attention to a linear consciousness of time, whereas these structures function in tandem with a variety of neuroendocrine processes which could underlie attention to a cyclical consciousness of time. The pineal gland is one candidate in this set of neuroendocrine processes.

The role of the neuroendocrine mechanisms in attentional processes has been well studied (e.g., Aeschbach et al., 2003; Carrier & Monk, 2000; Clynes, 1961; Halberg et al., 1961; Miller, Kastin, Sandman, Fink, & van Veen, 1974). However, a specific perceptual role for the pineal gland remains an enigma. Pineal functions have a considerable impact on chemical, electrical, and anatomical systems throughout the organism (Cardinali, 1983; Goldman, 1983; Reiter, 1981). Despite this pervasive influence, much like assumptions of "time" have been ignored (Slife, 1995), the role of the pineal gland in attentional mechanisms has previously been neglected by some investigators (Brain, 1958; Kinsbourne, 1974; Penfield, 1975) and actively rejected by others (Dennett & Kinsbourne, 1992; Edelman & Tononi, 2000; Mesulam, 1981). However, a putative role in sensory attention has been appreciated in modern times for a full two decades (Dawson, Crowne, & Richardson, 1986; Geschwind & Galaburda, 1985; Reinis & Goldman, 1982; Wetterberg, 1983).

The primary line of evidence for epithalamic (pineal) control of sensory awareness and behavioural responsiveness is evolutionary. The mammalian pinealocyte is appropriately included in Collin's sensory receptor cell line since it evolved from a photoreceptor element arising from a neuroepithelial evagination in the diencephalic roof of the third ventricle (Collin, 1979). The parietal eye contained in the pineal complex of lizards (often called the "third eye" in Eastern religious traditions) is a highly developed photoreceptor with a lens and a retina (Ralph, Firth, Gerr, & Owens, 1979).

For all species studied so far, the concentration of the pineal hormone melatonin increases during the dark phase of the environmental photoperiod. Despite distinct ancestry, the recurrent orbital path of the earth around

the sun has rendered the identical environmental pressures of alternating light and dark on all species. The common adaptation of melatonin increase during dark time by species of distinct ancestry is evolutionary convergence (Gern & Karn, 1983). The recurrent phenomenon of the photoperiod is well-represented internally by melatonin rhythms (Cardinali, 1981; Reiter, 1981). Melatonin is concentrated throughout many brain regions (Anton-Tay, Diaz, & Fernandez-Guardiola, 1971; Pang & Brown, 1983) and, since it is released into the cerebrospinal fluid and into the blood (Cardinali, 1981), it can be said that each part of the organism contains a representation of the pineal gland by a specific pattern of melatonin concentration that depends on the prevailing environmental conditions. This idea resembles Edelman and Tononi's (2000) suggestion that neuromodulators function according to a combinatorial matrix depending on their secretion and concentrations across brain regions.

Taking this evidence together, the pineal gland seems to be an integrative transduction system, responsible for transducing neuroelectrical information about light into hormonal signals (Cassone & Natesan, 1997). It seems to do this by synchronizing neurochemical (Cardinali, 1981; Quay, 1965), endocrine (Cardinali & Ritta, 1983; Reiter, 1983), motor (Dawson, 1990; Kovacs, Gajari, Telegdy, & Lissak, 1974; Quay, 1970a; Sampson & Bigelow, 1971), emotional (Datta & King, 1977), and intentional (Viader, Cambier, Masson, & Decroix, 1985) oscillations with respect to the photic environment—with the pineal hormone melatonin providing a measure of the duration of darkness to the organism (Binkley, 1982; Goldman, 1983; Reiter, 1981; Pang, Yu, & Tang, 1982).

The pineal gland regulates a variety of behavioural responses. This includes behaviours that vary with seasonal changes in photoperiod, such as migration and mating (Goldman, 1983; Menaker, Takahashi, & Eskin, 1978; Reiter, 1981), and with the time of day, such as sleeping (Anton-Tay et al., 1971; Mouret, 1982). In rats, pinealectomy can induce hypertension (Zanoboni & Zanoboni-Muciaccia, 1967) and alters the paradoxical sleep circadian rhythm by blocking its usual anticipatory increase in the hour preceding illumination onset, while not substantially affecting slow-wave sleep (Mouret, 1982). Administration of melatonin induces sleep in cats (Marczynski, Yamaguchi, Ling, & Grodzinska, 1964), produces extinction of passive avoidance and diminishes emotionality in rats (Datta & King, 1977), and reduces taste aversion in neophobic animals (Golus, McGee, & King, 1979).

As a model of Descartes' early suggestions that the pineal has a role in intentionally focusing attention (see Carter, 1983 quoted earlier), Dawson et al. (1986) studied visual, auditory, and tactile attention in the rat. While the studies already reviewed point to a

visuomotor orienting function for the pineal in rats, Dawson's studies suggest both an attentional and an emotional or conative role for the gland (e.g., Dawson et al., 1986). Additional studies (Dawson, 1986, unpublished Masters thesis) showed that pineal lesion suppressed visual orienting and spontaneous turning behaviour towards either side of the body. In addition, there was right sided neglect in response to bilateral visual stimulation. While this study was a replication of pilot research conducted earlier (Dawson et al., 1986), pineal lesion was found to reduce the attention level in comparison with sham but not in comparison with unoperated controls. Thus, it appears that pineal lesion reduced the hypervigilance often seen in response to trauma—in this case, in response to surgical stress.

In any case, the interpretation of pineal visual function is supported by demonstrations of pineal visual evoked potentials (Dafny, 1977; Reuss & Kiefer, 1989) and pineal modulation of neuroendocrine responses to visual stress (Klein, Siegel, Conforti, Feldman, & Chowers, 1979). Moreover, there is accumulating evidence that the pineal gland may also play a role in the momentary aspects of visual attention in humans (Brainard, Rollag, & Hanifin, 1997; Goldstein et al., 1989; Sandyk & Iacono, 1993). However, studies also indicate that in addition to the gland's role in visual function (Dawson et al., 1986), the pineal can modulate auditory (Dafny, 1977; Klein et al., 1979), and olfactory (Dafny, 1977) senses and these findings extend the purported behavioural function of the mammalian pineal gland to a polysensory modulation of attention.

The anatomical literature on the pineal reinforces its presumed sensory function in mammals (see Korf & Moller, 1984 for review). A neuronal pathway projects from the retina to the suprachiasmatic nucleus, through the lateral hypothalamus, descends through the reticular formation and ascends to synapse in the superior cervical ganglia in the spinal cord. From there, bilateral projections from the superior cervical ganglia (SCG) convey visual input to the pineal from the retina (Moore, 1980). There is strong evidence implicating modulation of pineal function by norepinephrine from SCG axon terminals—also suggesting a role for norepinephrine uptake in producing pineal dysfunction (Axelrod, 1974; Zigmund, Baldwin, & Bowers, 1985). This pathway, which ends in the transduction of photic signals into hormonal information, is characterized by central processing alternating with autonomic processing. There is evidence of central projections to the pineal from medial habenula (Dafny, 1983), habenular and posterior commissures (Buijs & Pevet, 1980; Dafny, 1980), and from the superior colliculi (Guillerot, Pfister, Muller, & DaLage, 1982). All taken together, this evidence suggests a role for the pineal gland in integrating a diversity of sensory signals into a coherent perception experienced as consciousness.

It is interesting that with the introduction of melatonin on a nightly basis, consciousness is lost to sleep, sensory responsiveness is lost, and bodily functions are entrusted to autonomic processes. With the decreasing secretion of melatonin as light intrudes, consciousness is regained and autonomic processes are once again rendered subject to voluntary monitoring and controls.

6. Melatonin and consciousness

Studies of the pineal suggest a role for melatonin in dark adaptation and object detection. There may also be a role in learning and memory, as melatonin has been found to hinder the formation of a conditioned reflex (Arushanyan & Vodolazhskaya, 1999). Consistent with this research, the alerting response to light has been shown to vary in a dose–response fashion with the degree of melatonin suppression by light (Cajochen, Zeitzer, Czeisler, & Dijk, 2000). Melatonin has also been suggested to play a role in degenerative states of the retina such as retinal dystrophy (Djamgoz, Hankins, Hirano, & Archer, 1997).

In addition, there is evidence for an important role of the pineal hormone melatonin in cognitive functioning more generally. The feeling of tiredness experienced as one approaches sleep is regulated by the hypothalamus in synchrony with the pineal gland's nightly secretion of the hormone melatonin. The inhibition of melatonin secretion with the onset of light each morning is thought to time the onset of activity after waking (Cassone & Natesan, 1997). Melatonin is known to have sedative–hypnotic effects and can resynchronize the sleep–wake cycle under conditions known to produce insomnia (Dawson, 1990; Skene et al., 1996). As such, melatonin has been termed a “dark hormone,” being released in synchrony with the onset of darkness and decreasing coincident with the onset of light. Thus, melatonin appears to regulate the synchronization of internal and external environments. This is albeit on a longer-term scale than momentary visual experiences, but is nevertheless a critical synchronizing signal to neurochemical mechanisms underlying wakefulness with a message to shut down.

Recently, Golombek et al. (1996) reviewed melatonin's inhibitory effects on consciousness such as sedation, hypnotic activity, pain threshold elevation, anti-convulsive activity, and anti-anxiety effects. They also review its direct effects on circadian rhythmicity through entrainment, resynchronization, alleviation of jet-lag symptoms, and phase-shifting. There is a clear time-dependency of some of these effects, a proposed interaction with the GABAergic system, and suggestions of the usefulness of pineal hormones as therapy for human disorders (Golombek et al., 1996). For example, melatonin treatment significantly decreased the

desynchronization between internal circadian rhythms and the external environment during jet-lag, shift-work, blindness, and delayed sleep phase insomnia (Skene et al., 1996).

Another area of recent research on melatonin is as a sleep-inducer in children. Because of the paucity of side-effects following melatonin administration, it is seen as a good alternative to pharmacological sedation and as a complementary method to sleep deprivation (Wassmer, Quinn, Whitehouse, & Seri, 2001). It has also been tested in a recent clinical trial at BC Children's Hospital in Vancouver and was shown to successfully reduce the chronic sleep disorders in children and adolescents with neurodevelopmental difficulties (Jan, Freeman, & Fast, 1999b; Jan et al., 2000). These difficulties, including blindness, mental retardation, autism, and so on, decrease the ability of the person to sense and interpret environmental cues which synchronize their sleep. Moreover, melatonin has been used to facilitate measurement of the circadian sleep–wake cycle with EEG after neuroleptic treatment in one case (Wirz-Justice, Cajochen, & Nussbaum, 1997) as well as in young adults (Nir et al., 1995) and in children with seizures (Jan, Connolly, Hamilton, Freeman, & Laudon, 1999a).

While melatonin has not been shown to be essential for circadian organization, it consistently reinforces functions associated with darkness and maintenance of synchrony with the solar day. Notably, melatonin responds to level of illumination (Dollins, Lynch, Wurtman, Deng, & Lieberman, 1993) and influences the timing of alertness, sleep, and waking (Arendt, Middleton, Stone, & Skene, 1999). But does this role generalize to the stabilization of temporal organization with development? Although it is not yet possible to answer this question with certainty, melatonin appears to have a role in a wide range of physiological systems (Golombek et al., 1996). As well, melatonin has been implicated in the timing of developmental milestones prenatally and in timing the onset of puberty and annual reproductive cycles in non-human animals (for review, see Arendt, 1997). These functional roles suggest safety concerns in the administration of melatonin to children and adolescents.

Its contribution to genetic transcription of neural proteins also suggests a key developmental role in timing changes in receptor binding sensitivity in the brain (von Gall et al., 2002). Recent attention has focussed on melatonin's utility in the pediatric population. Here, melatonin has been proposed as a marker of psychiatric conditions (Cavallo, 1993; Garcia-Patterson, Puig-Domingo, & Webb, 1996; Golombek et al., 1996; Skene et al., 1996), as a method to re-establish circadian rhythms after long exposure to artificial lighting (such as on intensive care units), and as a treatment for sleep disorders associated with developmental delay or blindness (Cavallo, 1993; Jan et al., 1999b). This collection of

findings argues against Arendt's (1997) conservative stance that there are insufficient data on the use of melatonin in organic or psychiatric disease for any evaluations to be made. However, further research is certainly recommended to clarify the roles of melatonin in the treatment of sleep disorders which are frequently seen concomitantly with psychiatric disturbances.

In summary, in addition to the dynamic loops between cortex and thalamus which may integrate the diversity of conscious experience (Edelman & Tononi, 2000), what appears to integrate the diversity of temporal systems is the system of internal biological clocks, with evidence suggesting the SCN and pineal play major roles. However, it is important to acknowledge other candidates for re-entraining or re-entrant loops. These include: neural autoreceptors, slow and fast-firing neurons, differing conduction delays, cyclic gene transcription, synaptic re-uptake, and the environmental influences of synchrony in the linguistic and social domains. The role of each of these in the temporal structure underlying the representation and integration of temporal experience is another interesting topic for further research but is beyond the scope of this paper.

7. Temporal organization

It should be noted that time can be viewed either as a sensory modality or an organizing principle. As a sensory modality, time can be treated as just another sense, like vision, audition, touch, taste, and smell. In the context of the binding problem, in contrast, time is much more useful as an organizing principle. The classical frame of the binding problem is: How can neural processes explain the perception of the unity of each experience when, at any given moment, there is a near-infinite number of possible objects of consciousness? Adding time as an organizing parameter to the binding problem yields a more intriguing question: How does time underlie the cause–effect relationships inherent in the integrated binding of diverse sensory elements of human experience? Therefore, we are left with the question of what causes these intricate neural processes to have the effect of an integrated sense of being aware of something. Without falling into infinite regress, the only rational remaining “cause” is ultimate. It is Time itself.

Time is ubiquitous. Reflections of time such as cause-and-effect, aging, the life cycle, and circadian rhythms such as the sleep–wake cycle are reasonably familiar phenomena to most people. For the scientist, on the other hand, most research examines time from a linear or Newtonian standpoint, both measuring and interpreting time as a one-directional linear flow from past through present to future, moving with a uniform rate that is applicable to everyone. Accordingly, in recent

computational models of cognition, semantic representations are without reference to time, essentially static, inert, and without history. It is widely acknowledged in physics, for example, that there is nothing that makes any particular direction of time more valid than any other. However, this standpoint ignores entropy, the arrow of biological time which leads dynamical systems inexorably toward equilibrium (e.g., Coveney & Highfield, 1990), and is fraught with other assumptions as well (Shanon, 1998).

For example, the Newtonian assumption of the linearity of time is contradicted by a preponderance of evidence supporting cyclicity as a more accurate temporal model of living systems (see Slife, 1995). However, the possibility exists that there may be two internal clocks governing time-sense, one reflecting linear time, the other cyclic time. This notion is supported by evidence that human beings gauge the passage of short and long durations using two different clocks, one corresponding to waketime, the other to body temperature (Aschoff, 1998; Campbell, Murphy, & Boothroyd, 2001). Moreover, following Crick and Koch (1998)'s review of experiments on "bistable percepts" and their importance in understanding the neural correlates of consciousness, it is important to note the bilaterality of past and future time about the figurative fulcrum of a fleeting "specious present" (James, 1891). Likewise, linear and cyclic time can be viewed as two prominent and stable perceptions of time which compete for attention. Indeed, the conventional notion of time as a one-directional flow is debated by studies suggesting the existence of bidirectional time (e.g., Dawson, 1992a, 1992b). Much like biological time which repeatedly flows "up" and "down" (i.e., in two directions), psychological time appears to have two prominent directions or "sides": one is accounted for by memory, which "looks" backward into the past; the other is explained by expectation, which "looks" into the future and sets goals (Cottle, 1968). Although recalled events are typically reported to be more significant than anticipated events (Dawson, 1992a; Fidler, Dawson, & Gallant, 1992), there is no reason to think that the processes of memory and anticipation are not carried on simultaneously, with one generally more available to awareness than the other. Not merely a philosophical point, this idea makes sense in terms of Edelman's re-entrant systems model (Edelman & Tononi, 2000) and is supported by evidence from fMRI studies showing that moral emotions activate subcortical areas at the same time as prefrontal cortex (Moll et al., 2002).

Due to this simultaneity, then, under certain conditions, cognitive functions such as memory and expectation can become confused—even non-existent—for example, during trauma, after consumption of a psychoactive drug, or during sleep, when the processes responsible for dissociating the perceptions of past and future are held at bay. Without a well-ordered percep-

tion of time which distinguishes memory from expectation—past experience from future plans—the differences among childhood experiences, recent events, and future goals might fade. The perceived context for action could even disappear, and events ordinarily perceived to take days, hours, or months could seem to occur within seconds—or vice versa, events that ordinarily take seconds could seem lengthened to years. It follows that experiences associated with a disruption or distortion of the perception of time could have a powerful impact on the individual, as well as an interest for researchers and clinicians.

However, it is important to say that none of this is certain. These statements are based only on presumed language with a social history that may not apply across all cultures. Indeed, there is a literature describing social-cognitive (Dawson, 2000; Summers & Dawson, 2000) and ethnic differences (Hall, 1984) in the perception of time. Thus, in an effort to develop a theory of brain-based temporal consciousness that applies to human beings across cultures, it is important to return to the evolution of the concept of time and its importance in promoting the biological ability of the species to survive and adapt to environmental demands.

The narrative construct of "time" emerged over the course of thousands of years during which human beings evolved and adapted to the fluctuations in daylight with the rotation of the Earth on its axis and the orbit of the Earth about the Sun. Indeed, at least since antiquity, "the Sun, the Moon, the . . . stars, which bear the appellation of 'planets,' came into existence for the determining and preserving of the numbers of Time" (Plato, 2001). For thousands of years, then, and in particular since the invention of the escapement mechanism in the 13th century, the wrist-watch and calendar have generally been taken to be reasonable approximations of astronomical events (e.g., Coveney & Highfield, 1990). If the motions of planets and the sun are modelled by such time-tools, and since planetary and stellar motions are cyclical, then linear time is almost certainly a mistaken assumption. Thus, these tools are used to provide an oversimplified and imperfect social agreement about the definition and determination of time. They model the correspondence or degree of synchrony of the internal cognitive map with a cyclical, non-linear external environment, but do so in an incomplete fashion—missing, for example, the transient fluctuations between light and dark at dawn and dusk and the predictable seasonal transitions in light and temperature that can only be experienced in a recurring organic present. These phenomena arguably occur throughout the human species, regardless of cultural or linguistic influences, even though ways of describing them might differ by region and experience.

A great deal of research on biological rhythms indicates convincingly that a set of internal clocks evolved in response to these recurrent environmental cycles. These

internal clocks generate overt cycles in physiological and behavioural events and time the frequencies of these events quite precisely (e.g., Mouret, 1982; Pittendrigh & Daan, 1974). This precision arises primarily under the regulation of environmental time cues or “Zeitgebers” such as daylight alternating systematically with the darkness of night. In the absence of a light/dark cycle, though, the overt rhythm is thought to reflect directly the generator function of an internal circadian clock in a “free-running” rhythm (Aschoff & Wever, 1976). Another reflection of an internal clock appears, for example, when a photocycle reversal occurs (such as during night-shift or long jet-flights). When this occurs, the coincidence of external time cues and behaviour is transiently lost and remains inexact until resynchronization or “re-entrainment” to the new time cues is achieved. Thus, the internal clock can function independently of environmental stimuli and this function is modulated by an endogenous neuroendocrine timing system that has adapted to synchronize sensory awareness and behaviour with external time cues. As such, the temporal organization of the brain serves to integrate diverse elements across developmental time and places the person in a particular subjective time-frame. This begins to describe the role of internal clock system as an extension of Edelman’s dynamic core.

So far, then, I have reviewed evidence suggesting that to coherently bind or unify the diversity of phenomenological experience, some form of temporal tagging or sensitivity to repetition across time is required (Alais et al., 1998; Edelman & Tononi, 2000; Henson, 1998; Rickert et al., 1998). If tagging is absent, or progressively degenerating, the person (such as in Alzheimer’s disease) would not know *when* the experience occurred and would be insensitive to recognition or recall of past events, and would not distinguish these from anticipations or expectations of similar events in the future. They would have difficulty placing themselves in time. Indeed, Damasio (2002) reports an amnesia patient who lives in a “permanent present.” The hippocampus, basal forebrain, and temporal lobes (which are damaged in this patient) have been identified in neuro-imaging studies as important for tagging when cognitive events occur in time. It has been known for some time that when the hippocampus is impaired, patients have difficulty retaining new memories for longer than about a minute. This is called anterograde amnesia. When parts of the temporal cortex are damaged, on the other hand, patients seem unable to recover long-term memories—this condition being known as retrograde amnesia. Thus, the temporal lobe and its subcortical partner (the hippocampus) seem to be responsible for tagging events with specific references to the relative timing of phenomenological experience.

According to Damasio (2002), these structures participate in “mind time” which represents the phenome-

nal content of everyday questions like “When did I get married? When were my children born? and How old am I?” The patient discussed above could not answer these questions. However, his biological cycles were well-organized (Damasio, 2002). While it might be tempting to separate the circadian “body time” from a “mind time,” this would be a mistake paralleling “Descartes’ Error” which inaccurately separated the mind from the body (Damasio, 1994). While presuming the separation of “mind” from “body” based on a single case, separating body-time from mind-time would also ignore the possible existence of neural networks and neurochemical interrelationships among these networks in the organization of temporal consciousness. Furthermore, evidence for consciousness as a hierarchical and reciprocally interactive whole would be neglected (see, for example, Edelman & Tononi, 2000).

The large literature supporting the roles of the hippocampus, basal forebrain, and temporal cortex in the temporal organization of cognition has only been briefly summarized here. Further explanation is beyond the scope of this paper which rests primarily on a description of neuroendocrine mechanisms underlying the experience of time—and on the cognitive implications of this temporal organization of the brain. Thus, research reviewed here suggests the neuroendocrine pathways involving the SCN, pineal gland, and melatonin should be appended to our understanding of the temporal organization of the brain and consciousness more generally. It is an interesting hypothesis that these structures might interact in a core temporal structure which maintains temporal coherence in a personally experienced “present” despite the enormous potential number of times in which we might find ourselves, even within a single day.

Two additional points emerge with respect to the neurophysiological organization of time. First, brain regions other than those located in Edelman’s proposed corticothalamic dynamic core have been found to be critical in marking the timing of events. For events to have a coherent “flow” that is ordinarily ascribed to consciousness, there must be brain structures which generate an internal model of the external world in terms of time. Indeed, such structures are the hippocampus, amygdala, hypothalamus, reticular activating system, and the epithalamus (commonly called the “pineal gland”). These regions presumably provide a kind of background for predicting events and preparing consciousness to interpret incoming sensory-perceptual experience.

In terms of motor processing, the central role of the cerebellum in time estimation—as a primary source of temporal codes—has been reinforced by recent research (Lalonde & Hannequin, 1999; Tracy, Faro, Mohamed, Pinsk, & Pinus, 2000). Likewise, studies of the timing of movements in dyslexia, Parkinson’s

disease, and developmental coordination disorders have implicated both the cerebellum (Nicolson, Fawcett, & Dean, 1995; Volman & Geuze, 1998) and the basal ganglia (Lalonde & Hannequin, 1999; Wing, Keele, & Margolin, 1984). Along with these brain regions, the prefrontal, sensorimotor, and temporal cortices have been shown to be involved in self-paced and primary time estimation (Ortuno et al., 2002; Rivkin et al., 2003; Tracy et al., 2000). Thus, the areas of the brain concerned with temporal tagging and sensorimotor synchronization may be *the* part of the dynamic core that underlies the critical and predictable return of consciousness to specific stimuli on a minute-by-minute, hourly, or daily basis. In this way, a well-integrated experience of a flow of consciousness through time is formed.

So far, we can take from these studies the suggestion that temporal tagging could be an important component process in binding or integrating diverse elements of perceptual experience across development. In addition, there appear to be numerous brain structures responsible for binding experience in memory and sleep, with experience that runs on a moment-by-moment basis while keeping these various levels of experience in synchrony with the rhythms of nature and movement. Indeed, as Melges and Fraser have suggested, the entire brain may be involved. An understanding of what the brain is doing to accomplish this feat is only beginning.

8. Temporal disorganization

When the integrative relationships between the various representations of time are disrupted, temporal disorganization is the result. Aging, drug-induced altered states of consciousness, and mental illness are all discussed as examples of symptoms of disorganized temporality. For the following sections, it may be helpful for the reader to remember an over-simplified, but guiding concept: When mechanisms underlying linear cause-and-effect are turned off, mechanisms underlying cyclicity are turned on—and vice versa. The situation is admittedly more complicated, however, as this dichotomous heuristic does not account for sporadic, chaotic, or random behaviour seen in disrupted sleep cycles in the elderly or for “time-transcendence” (Kastenbaum, 1989) seen in dementias or psychoses. Even so, in general, the heuristic should help the reader to remember that temporal organization has various sources, and disruption of any particular source might have reciprocal or otherwise differing effects. Evidence for the disruptions listed will not include an analysis of the relative contribution of the various components of the dynamical mechanisms underlying temporal consciousness.

9. Temporal disorganization in aging

Temporal disorganization becomes most apparent when one examines the literature on aging. It is supposed by experts in the field of biological rhythms that the circadian (about 24 h) cycle can furnish information that can be used to control or even alleviate behavioural deficiencies that arise as the life cycle nears its end (e.g., Samis, 1978). Temporal disorganization during old age includes: a non-linear age-related increase in the subjective rate of time passage (Fraisse, 1963; Gallant, Fidler, & Dawson, 1991; Janet, 1877), a decline in future perspective (Dawson, 1992b; Fidler et al., 1992; Frank, 1939; Janet, 1877), and a decay of the sleep–wake cycle (Dawson & Crowne, 1988; Dawson, Crowne, Richardson, & Anderson, 1987; Jones, Kimeldorf, Rubadeau, & Castanera, 1953; Peng & Kang, 1984; Richter, 1927; Samis, 1978; Slonaker, 1912; Wax & Goodrick, 1978; Welsh, Richardson, & Dement, 1985). Taken along with recent findings of clock genes (Piggins, 2002; von Gall et al., 2002), these penultimate changes support Samis’ (1969) claim that temporal disorganization is a hallmark of the aging process.

Where consciousness undergoes most change is over the course of development, both through childhood as linear cause–effect relations are learned and encoded in the brain, and later during old age—when fluid intelligence, cause–effect relations, and circadian organization tend to break down. Based on the evidence for physiological underpinnings of temporal organization in brain structures and processes already described, it is logical to suppose that these symptoms of temporal disorganization have their source in dysfunction residing in these same structures and processes. For example, like so many other areas of the brain, the pineal gland has developmental significance as its concentrations of indoleamines, catecholamines, and melatonin decline over the life span (Tang, Hadjiconstantinou, & Pang, 1985). Based on the pineal’s hypothesized connection to attentional processes discussed earlier, this may relate to decrements in attention known to occur with increasing age (James, 1891; LeVere, 1983). There is evidence that the pineal and melatonin may play a role in stabilizing behavioural cycles that decline as a function of age (Armstrong & Redman, 1991; Dawson, 1990; Quay, 1972; Ruzsas & Mess, 2000), and this may relate to early wakening and sleep disorders in the elderly. In addition, deterioration of the SCN may be associated with sporadic sleep over the 24-h period (Bliwise, Rye, Dihenia, & Gurecki, 2002; Mishima, Okawa, Hisumi, & Hishikawa, 2000), whereas an age-related decline in the ability to phase-shift to a change in the photoperiod seems to reside in the pineal gland (Dawson, 1990; Quay, 1970a, 1970b, 1972) and its hormone melatonin (Skene, Lockley, & Arendt, 1999).

10. Temporal disorganization in drug-induced altered states of consciousness

Although sedative and hypnotic drugs are well-known to alter the perception of time (e.g., Rammsayer, 1999), aside from its effects on the timing of sleep, the effects of melatonin on temporal organization of consciousness have not been studied. However, a chemically related class of substances are the indoleamine psychedelics. The psychedelics (including LSD and psilocybin) are perhaps best known for inducing potent changes in the cognitive organization of time that are memorable for many years after intoxication. Some recent case studies support this well-documented effect on cognitive time distortion in LSD intoxication (Dawson, 2001; Hayes, 2000). Likewise, Strassman (2000) posits pineal dimethyltryptamine (DMT) as a so-called “spirit molecule” responsible for experiences of a timeless and “eternal presence.” Baruss and Vletas (2003) also examine temporal disorganization during altered consciousness that results from ingestion of psychedelic drugs.

An important caution to be taken from this research is that the scientist-practitioner must separate the temporal effects of drug use from temporal disorganization in the absence of drugs. Even so, research studies of psychedelics carry important clinical and pharmaceutical implications for assessing and treating those individuals who report using psychedelics, including marijuana (Melges, Tinklenberg, Hollister, & Gillespie, 1970).

11. Temporal disorganization in mental illness

Various disruptions in the brain’s organization of time have already been mentioned. These have important clinical implications, particularly in facilitating our understanding of the desynchronization or “unbinding” of consciousness seen in certain mental illnesses. Such mental illnesses include insomnia, amnesia, pain sensitivity, inattention, and degenerative disease. Acknowledging overlapping dynamics among different clinical conditions, from this point onwards, I will focus strictly on temporal disruptions which occur during psychological disorders. The implications of these will hopefully shed light on the temporal organization of cognitive status.

Before beginning this section of the review, however, it is important to point out a rather basic assumption. That is, the term “disorder” (APA, 2000)—as widely used in the Diagnostic and Statistical Manual (DSM-IV-TR)—strongly implies a temporal problem. A sense that things are “disordered” can convey a sense of things being “out of order,” “in the wrong order,” or not occurring in the expected sequence, at the expected time,

and the like. Thus, considered broadly, the global use of the term “disorder” in reference to psychiatric or psychological dysfunction can already be viewed as pointing to temporal disorganization as a strong association (even if it is not causative) of psychological problems.

However, while not relying on this general observation as a proof—but as an assumption—of this principle, it remains important to present a wide array of psychological disorders which can be identified as associated with difficulties in temporal binding or in temporal organization. Assuming also that psychological disorders are symptomatic of altered consciousness, identifying the array of disorders associated with *temporal* changes in consciousness would strongly suggest that the temporal organization of consciousness is an important phenomenon in clinical assessment and treatment planning.

Following these assumptions then, the examples of psychological disorders provided below are those in which literature could be found which described evidence of changes in temporal organization of brain, behaviour, and cognition. Exclusions include, for example, attachment disorder and personality disorder. Even though there are changes in temporal organization in attachment disorders and personality disorders (Dapkus, 1985), these are not included here due to a lack of documented temporal changes in the brain in these disorders. Another exclusion from this section is sleep disorders—except as they appear below in a theory of anxiety—as they have been referred to already.

This is not an exhaustive list. Because my own research program on time extends back some 20 years, the search strategies used to yield these references took place correspondingly over a period of many years using such indexes as PubMed, PsycInfo, as well as manual searches through Index Medicus and Social Sciences Citation Index. Key terms searched included “temporal organization,” “temporal disorganization,” “time and psychological disorders,” and “time and x” (where x is the disorder of interest).

11.1. Attention deficit hyperactivity disorder

One condition eliciting substantial clinical concern in recent years is Attention deficit hyperactivity disorder (ADHD). ADHD is characterized by a behavioural inhibition syndrome which prevents a child from inhibiting spontaneous behavioural responding. The child with ADHD is extremely distractible, unable to focus, and unable to sit still. Difficulty organizing, scheduling, or planning for the future is often seen in ADHD, suggesting a failure of temporal organization or “time blindness” (Barkley, 1997). Disruptions in the ability to reproduce durations have been found in ADHD children, especially when distracted (Barkley, Koplowitz, Anderson, & McMurray, 1997). In addition, there is

evidence for dysfunction of the hypothalamic–pituitary–adrenal axis (Kaneko, Hoshino, Hashimoto, Okano, & Kumashiro, 1993), suggesting a hormonal modulation of impulsive behaviour in ADHD. In one case study, sleep difficulties seen in ADHD were treated successfully using chronotherapy combined with behaviour modification (Dahl, Pelham, & Wierson, 1991). Often successfully treated by stimulants that mimic the activity of dopamine in the brain, children with ADHD may show disruption of circadian timing with sleeplessness as a side effect of stimulant medication. As already mentioned, clinical trials with melatonin as an innocuous sedative have shown promise (Jan et al., 2000) but more research using melatonin agonists and antagonists should be done.

11.2. Autism

Studies examining the rhythmic organization of stereotyped behaviours found in autism have found that periodicity may appear in some behaviours (like rocking) but not in others (Ross, Yu, & Kropla, 1998). However, the possibility that temporal disorganization might be involved in the neurophysiological etiology of autism comes from findings of differing circadian patterns of melatonin correlated with EEG changes in young adults with autism (Nir et al., 1995). Melatonin treatment has had success in treating disrupted sleep–wake cycle in at least one case study of autism (Hayashi, 2000). Moreover, providing evidence for the putative influence of brain oscillators on perceptual binding, Grice et al. (2001) have recently demonstrated abnormalities in gamma-band EEG (about 40 Hz) that differed between autism and Williams syndrome. To account for the social timing deficits in autism, anomalies in clock genes may underlie these manifestations of temporal disorganization (Wimporoy, Nicholas, & Nash, 2002).

11.3. Schizophrenia

The human clock gene is also being studied in relation to the etiology of schizophrenia (Saleem et al., 2001). Other indications of temporal disorganization in schizophrenia include decreases in circulating melatonin levels, combined with difficulties falling asleep (Vigano et al., 2001). In a randomized, double-blind, cross-over clinical trial on 19 patients diagnosed with schizophrenia, melatonin significantly improved sleep (Shamir, Rotenberg, Laudon, Zisapel, & Elizur, 2000). Abnormally high prolactin levels in schizophrenia also suggest marked neuroendocrine disturbances (Vigano et al., 2001).

Another study looked at the disability in social skills in schizophrenia patients. This disability is widely treated by helping patients to structure or organize their

activities throughout the day. One study used actigraphy to study temporal organization of activity and rest and showed that a patient with chronic schizophrenia had a highly irregular temporal structure, as well as delayed sleep-phase insomnia (Haug, Wirz-Justice, & Rossler, 2000).

Persons with schizophrenia are known for their disorientation in time. The passage of time can vary significantly, with days seeming like months, weeks, hours, or even seconds. As well, the ability to order and predict events in time is compromised (Dapkus, 1985), but the literature is conflicting on the association of temporal disorientation and intellectual abilities. In one study, temporal disorientation about age was not found to be associated with pre-morbid intellectual impairment or past medical treatment (Buhrich, Crow, Johnstone, & Owens, 1988). In other studies, temporal disorientation was found to be associated with global intellectual impairment (Liddle & Crow, 1984) but not with the content of spiritual or religious delusions (Applebaum, Robbins, & Roth, 1999).

Prior time information (related to a duration yet to be experienced) and posterior time information (related to a duration being currently experienced) appear to be reversed in schizophrenics. For example, brain laterality associated with time information has been found to be a mirror image of non-schizophrenics (Mo, 1990). Other studies propose psychotic thought as a mode in which continuity, successivity, and simultaneity are not recognized (Morin, 1995). The non-unitary nature of delusions is emphasized (Brockington, 1991), thus implying that psychotic thought is disintegrated and lacks “temporal binding.”

11.4. Anxiety disorders

Based on their review of the animal literature, Golombek et al. (1996) have suggested melatonin has anti-anxiety effects. But regarding anxiety disorders such as obsessive–compulsive and panic disorders, evidence for the involvement of melatonin appears to be largely negative (Hajak et al., 1997; Millet et al., 1998). Even so, this does not discount some form of temporal disorganization that does not involve melatonin. For example, Dapkus (1985) has proposed that obsessive–compulsive disorder is characterized by a fixation to time. Likewise, there is a temporal relationship between panic onset and the avoidance of inescapable situations observed in agoraphobia (Thyer & Himle, 1985).

Posttraumatic stress disorder (PTSD) is another anxiety disorder for which there is no evidence of association with changes in melatonin. However, PTSD is—by its very name—characterized by temporal disorganization. According to the DSM-IV-TR, PTSD occurs in a situation that provokes an intense fear for one's own life or the life of another. Helplessness and horror

are associated emotions, and in children, agitation or disorganized behaviour can reflect a posttraumatic response. This includes symptoms of loosening of cause–effect relations as characterized by disrupted “temporal binding” as described earlier. Such temporally disorganized symptoms include recurrent memories and dreams or flashbacks, associational cueing through resemblance, and disorganized behaviour. Likewise, PTSD is characterized by recurrent and intrusive memories of the event, including repetitive play in which the trauma is re-enacted over and over again. Recurrence is often internalized in the dreams of the individual, at times without a report of a coherent context or meaning of the dreams. A sense of reliving the trauma, including “illusions, hallucinations, and dissociative flashback episodes” can also occur (APA, 2000). On exposure to cues that resemble or symbolize the traumatic event, severe psychological distress or reactivity can appear. In contrast, and at the same time, the individual engages in denial or avoidance of stimuli associated with the trauma by removing themselves from the person or thing that reminded them of the event, avoids or denies any memory of the event, and experiences a sense of foreshortened future (APA, 2000). In PTSD, difficulties associated with changes in consciousness include difficulties getting to or staying asleep.

Frequently, yet unfortunately, PTSD is the reason for removal of children from their parents’ care and, as a result, attachment disorders can overlap with PTSD. Effects of trauma on the subcortical regions of the brain are beginning to be mapped, though little is known about the precise changes in the structure of the brain as yet. In recent studies, life-threatening stress has been shown to reconfigure the molecular organization of these regions (see Teicher, 2002 for review). Teicher (2002) has suggested that experience is changed in a manner that prepares the individual to adapt in a dangerous world. This change is thought to be mediated by long-term increases in secretion of cortisol, a hormone which may be toxic to the brain (Carrion et al., 2002). As a result, brain damage can occur and, in some cases, the cost is a tendency towards violence that may not be reversible (Teicher, 2002).

Anxiety disorders have been related to circadian disorganization. However, consistent with well-validated cognitive models of anxiety disorders, recent research suggests that the role of cognitive attributions about sleep might play a larger role than the disorganization of underlying temporal mechanisms in the etiology of anxiety disorders. For example, Harvey (2002) suggests a reciprocal and inverse relationship between insomnia and anxiety level which is governed by cognitive attributions and emotional arousal. This reciprocal relationship is mediated by excessively negative cognitive activity which triggers autonomic arousal and emotional distress (Harvey, 2002). Selective attention to sleep-related threat cues may lead to an overestimate of

the perceived effect of lack of sleep on daytime performance. Escalating arousal and distress may spiral into a very real deficit in sleep and daytime functioning.

11.5. *Affective disorders*

Temporal disorganization at the seasonal scale is well-known in seasonal affective disorder (e.g., Lam & Levitt, 1999; Terman & Terman, 1999). Temporally disorganized circadian rhythms have been widely acknowledged in affective illness and phototherapy can be either a trigger or treatment for depressive episodes (Wehr, Rosenthal, & Sack, 1988). Hypotheses of affective illness based on the temporal structure of circadian rhythms include the abnormal free-run, phase advance, phase instability, and reduced amplitude hypotheses (Yamada & Takahashi, 1994). Furthermore, the human clock gene has been proposed to underlie changes in circadian rhythms in cyclic mood disorders such as bipolar illness (e.g., Saleem et al., 2001). This may relate to children with rapid cycling mood disorder whose sleep disorders were helped by melatonin administration (Jan et al., 1994).

Frequency differences can reflect changes in temporal organization as well. For example, depression scores are associated with low estimates of frequency with which positive events happen to oneself and high estimates of the frequency with which negative events happen to oneself and others (Kaney, Bowen-Jones, Dewey, & Bentall, 1997). It follows that positive events could be bound through inappropriately low frequency estimates and negative events could be bound by inappropriately high frequency estimates. In addition, future orientation tends to shorten in depression and to lengthen, on the other hand, in mania (Melges, 1989).

Temporal disorganization can include the belief that life is over. Distinct from the depression which culminates in suicidality, one case study examined three individuals with right frontotemporal structural lesions who developed the delusion of being dead known as Cotard’s syndrome (Pearn & Gardner-Thorpe, 2002). Loss of facial memory (Leafhead & Kopelman, 1997) and co-morbid depression have been found to be associated with Cotard’s nihilistic death delusion (Hansen & Bolwig, 1998). Descartes’ “cogito” (extreme doubt) provides an analogy to Cotard’s syndrome including non-existence of the world and self (Jalley, 1994).

11.6. *Spiritual problems*

Spiritual issues might also include differences in temporal organization. Whatever their convictions, experiences in which persons either feel “at one with God” or “abandoned by God” can bring on overwhelming feelings, and can disintegrate or “unbind” previous belief systems about a person’s place in ordinary time (see Wulff, 2000). The non-linear time of the right

hemisphere has been suggested as an important aspect of temporal organization in people with mystical experiences (Wulff, 2000). Brain changes in such “spiritual” states are exemplified in recent brain imaging studies of yogi’s, nuns, and Monks in deep prayer or meditation (Newburg, 2002).

11.7. *Dissociative fugue, amnesia, and identity disorder*

In their study of dissociative identity disorder, Van der Hart and Steele (1997) utilize Paul Janet’s distinction between placing some accounts of events too high in the hierarchy of perceived reality, and placing other explanations too low. In their study, they address ways in which traumatic memories can interfere with the normal sense of time. Therapeutic recommendations include reorganizing the phase relationships between events.

In addition, Edelman and Tononi (2000) propose dissociative states of amnesia support their model of the dynamic core. Indeed, they propose that a major functional split within the dynamic core would be expected in the case of split brain surgery or other neurological disconnection syndromes. Psychological trauma, dissociation syndromes, and schizophrenia might also be conditions in which a previously single, dominant dynamic core splits into two or more “subcores” (p. 152). A more discrete explanation comes from Forrest (2001) who proposes that the orbitofrontal cortex has a protective inhibitory role in temporal organization. According to this notion, sensitivity of this area of the brain to discontinuity in the early caregiving experience may, in the case of dissociative identity disorder, be responsible for the lateral inhibition between differing self-representations which in normal individuals remains integrated in a unified concept of self.

11.8. *Alzheimer’s disease*

Damasio (2002) describes the faulty placement in time seen in Alzheimer’s disease and there are well-known changes to the brain in these patients. These changes include dendritic plaques and tangles in structures responsible for memory such as cerebral cortex and hippocampus. Sundowning—defined as the exacerbation of Alzheimer’s symptoms in the afternoon or evening—has also been tied to disorganized circadian rhythms (Volicer, Harper, Manning, & Satlin, 2001), decreased melatonin secretion, and indications of successful treatment with melatonin (Cardinali, Brusco, Liberzuck, & Furio, 2002; Mishima et al., 2000).

12. Conclusion

Consistent with recent thinking, biological clocks are connected in a system of chaotic attractors (Glass &

Mackey, 1988). For example, one set of clocks is responsible for regulating the biological need for sleep, food, and reproduction. Other clocks regulate neural loops that together form memories, consciousness, and time perception at various scales. When the organization of these clocks moves out of alignment, both physical and mental illness can occur. The most direct manifestations of changes in the organization of these clocks is in the relative timing of biological needs, memories of recalled events, attention to when events are occurring, and expectations of when events are most likely to occur. Of most interest to psychology and psychiatry, these manifestations of temporal organization have developmental significance and are often disrupted in both ordinary changes in consciousness and in mental illness.

A broad range of psychiatric disorders have been reviewed, all of which have documented physiological evidence of temporal disorganization. Is it possible that the temporal mechanisms of the brain could be a common factor underlying these ailments? Melges (1989) points out that “time distortions may be a manifestation of, or a mechanism for, mental illness” (p. 99). In summary and according to Melges, sequencing problems are common in organic brain disease and psychosis, problems with rate are often seen in bipolar disorders, and difficulties with temporal perspective have been associated with borderline personality disorders. These are in addition to the manifestations of temporal disorientation in mental illnesses already discussed. Thus, it is an important question to explore whether treatment interventions could benefit by taking this into account.

The wide range of mental illnesses associated with temporal breakdown strengthens the likelihood that time is an important etiological factor underlying mental illness (e.g., Armstrong & Redman, 1991; Cavallo, 1993; Garcia-Patterson et al., 1996; Golombek et al., 1996; Pacchierotti, Iapichino, Bossini, Pieraccini, & Castrogiovanni, 2001; Skene et al., 1996). In addition, recent genetic studies suggest mutations in the human clock gene are at least partially responsible for changes in temporal organization seen in autism, schizophrenia, and bipolar illness (Saleem et al., 2001; Wimpory et al., 2002). Thus, the primary purpose of the present paper has been to show that time is—through its physiological manifestations—a unifying and binding element for the diversity of conscious experience. For example, when the unison of genetic, neurochemical, or hormonal time is disorganized, cognitions are also very likely to be experienced as disorganized or chaotic (Shanon, 1998; Shanon, 2001). Therefore, the relative contributions of genetics and environment to the organization of the various available parameters and values of time have important implications for improving our understanding of the assessment and treatment of mental illness, and the possibility of recovery from it.

The practical importance of this research stream includes the widening clinical application of melatonin to its immunosupportive and hypnotic properties (Bergstrom & Hakanson, 1998; Pierpaoli, Regelson, & Fabris, 1993; Reiter, 2003). As these new applications emerge and undergo scientific investigation, clinicians will increase their awareness about the effects of pharmacological and cognitive-behavioural interventions on the temporal organization of consciousness. The relevance of pineal function, melatonin, and temporal cognition to basic questions about consciousness and to clinical applications in medical and mental health contexts increases the importance of research on these matters.

In conclusion, then, this paper has hopefully shown that time is a binding principle for organizing conscious experience. It has physiological markers which function by attempting to synchronize the genetic, hormonal, neurochemical, neuroelectrical, behavioural, and environmental dimensions impinging on the identified person. As these dimensions interact, their reciprocal influences tag each other and the matrix of these tags correspond to a spatiotemporal code (i.e., in the language of physics, this is the “world-line” of the individual). A vast diversity of temporal meanings is derived from this code as the brain processes and translates it into useful information through “re-entrant pathways.” These meanings are then integrated to provide each individual with a coherent temporal signature which—in narrative terms—tells the person “that was in the past,” “the time is right,” “it is not time yet,” and so on. This ultimately brings uniqueness, harmony, and unison to the specific interactions identified with an individual’s life. When neuroendocrine pathways which are responsible for synchronizing consciousness with its various available environments are disrupted, changes in consciousness and mental illness are more likely to be observed.

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