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The Need for XR-Measurement of Decision-Making Decline and Conscious-State Transition Impairment before Nonvoluntary Euthanization of Dementia Patients

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Abstract

Non-voluntary euthanization of dementia patients, the majority of whom are severely conscious-state transition-impaired because of both high levels of anti-somnogenic cytokine levels and circadian disruption, indicates the lack of measurement of decision-making decline and conscious-state transition in palliative care settings. This chapter explains why and how to setup medically-meaningful tests to collect these measurements based on environmental-interactive parameters of nonconscious testing in circadian calibrated XR or virtual reality platforms. It also mentions worthy opportunities in relationship to the Human Connectome Project, including the Alzheimer's Disease Connectome Project.

Keywords: dementia, euthanization, virtual reality, XR, human connectome project, Alzheimer's Disease, conscious-state transition, decision-making incompetence

1. Introduction

Dementia is a prominent symptom of various diseases and not just a disease in and of itself. It is part of brain disease transition such as following virus-infected inflammation through increased neurodegeneration and brain network dysfunctioning.

It renders difficulty in recognition and response to daily environmental information which are needed in short-term learning and recall and decision-making [1, 2]. In general, one of the most disturbing characteristics of neuroinflammatory diseases is loss of conscious-state transition [3]. This is a type of disability or impairment that results in the presence of persistently high levels of anti-somnogenic cytokines [4, 5], and common to Alzheimer's Disease patients [6]. It is also associated with disruption of circadian synchronization between neuronal networks of the brain [7, 8].

A dementia patient's care-giving team is presumed to include certified doctors and nurses qualified in early diagnosis and strategies for dementia-symptom management. The targets of such caregiving include optimizing physical health, cognition, activity and well-being identifying and treating accompanying physical illness detecting and treating challenging behavioral and psychological symptoms providing information and long-term support to carers (WHO).

Section 4.1 of the Dutch euthanization law [9] declares that euthanasia may be given to a patient who is no longer mentally competent as a result of advanced dementia, and that the doctor does not need to agree with the patient regarding the time or manner of euthanatic execution based on a physician declaration of patient inability to comprehend the subject.

Euthanization is delivered via anesthetics without acknowledging the surge of neurophysiological coherence and connectivity in the forced-dying brain [10] or on the basis of any measured disability of a patient to change from one conscious-state to any other. The degree that sensory information processing and conscious memory, awareness, learning and recall are supposed to be fully disabled [11] by the simple observation of delirium seems to possibly have led to an unchecked medical assumption that an overdosage of anesthetic-euthanatic neurotoxins is sufficient to overcome the disability and trigger instant brain death. However, the research shows that this is invalid and that memory formation- and indeed, brain survival mechanisms - are evolved to be much smarter, enabling survival-related learning related neuronal synaptic plasticity changes to occur even under deep anesthesia [12, 13].

In 2019, 146 dementia patients were euthanized in the Netherlands, 14% less frequently than the previous year [14].

The English version Regional Euthanization Review Committees- The Netherlands, report (2018) [9] states that.

Dementia

Two notifications in 2018 involved patients in an advanced or very advanced stage of dementia who were no longer able to communicate regarding their request and in whose cases the advance directive was decisive in establishing whether the request was voluntary and well considered. See case 2018-41, described in Chapter II, and case 2018-21, published on www.euthanasiecommissie.nl.

In 144 cases the patient's suffering was caused by early-stage dementia. These patients still had insight into their condition and its symptoms, such as loss of bearings and personality changes. They were deemed decisionally competent with regard to their request because they could still grasp its implications. Case 2018-123, described in Chapter II, is an example.

But, the section titled Advanced Directive Points to Consider (Section 4.1, f, (see Annual Reports, Dutch Euthanasia Committee [15]) requires physicians to answer: *Are there any contraindications that are inconsistent with the advance directive and preclude the performance of euthanasia?*

If so, this statement represents one opportunity to provide an argument that all dementia patients deserve medically-meaningful conscious-state transition monitoring and decision-competence evidence before non-voluntary euthanization can be legally authorized.

Such monitoring technology would enable demonstration of key factors of non-eligibility when a patient is unable to transition into unconsciousness or brain death instantaneously or for up to 36 hours - even following severe anesthesia and cardiac

arrest [16] simply because of the nature of the disease’s impact on the brain (see **Figure 1** below).

The euthanization method which is intended as a pain-free killing is error-prone with patient re-awakening rather than instant dying [17, 18] on record. Anesthetic drugs targeted to ion channels affect neuronal activity in the Central Nervous System (including the brain), the peripheral nervous system (PNS) and all connected organs, and the cardiovascular system [19]. Barbiturates such as pentobarbital suppress the central nervous system (CNS) by binding to gamma-aminobutyric acid (GABA) A subtype receptors, alters inhibitory postsynaptic CL⁻ currents while simultaneously inhibiting excitatory presynaptic nerve terminal signal event transmission. This is supposed to sustain the opening of chloride channels and results in the suppressed neuronal activation of oscillations throughout the brain and sensory management throughout the entire system [20–23]. The GABAergic thalamic neurons would also therefore inhibit retinally-driven activity, and likewise disable input to the geniculo-hypothalamic pathway which is activated by crossed retinal inputs leading to the suprachiasmatic nucleus (SCN). In this way, brainwave activities related to conscious-state transition and measured by Bispectral Index (BIS) monitors [24] or Guedel’s classification system [25] are logistically absent, thereby theoretically preventing patient awakening and patient awareness or memory.

However, the research shows that brain death and cardiac death are not simultaneously correlated [26–29]). In research review by Robijn (2020) as part of an academic thesis submission, Robijn reports correlation between BIS and the Richmond Agitation-Sedation Scale (RASS) ($p < 0.0004$) including reporting patients ‘awake’ during euthanization despite observational physician [30] decisions that the patients were dead [31, 32]. Also, memory formation also continues under anaesthesia [12, 33, 34]. On closer inspection of the events, one finds that the high dosage anesthetics such as 9 mg/L pentobarbital intravenous injection used in euthanization in the Netherlands has explicit pharmacological warnings that the neurotoxic compound cannot reach the brain in one minute intravenous application and that that the accelerated injection causes gangrene, body-wide joint pain and tissue irritation for any intravenous-administered dosages above 0.5 mg/l. Furthermore, it reduces IL-1beta cytokine release by only 30–40%, while endogenous tumor necrosis factor (TNF- α) transport becomes elevated in a process that remains

Figure 1.
A list of features in the progression of amnesiac-related brain inflammation from disease or neurological disorders leading to risks that may compromise euthanization patient safety.

persistent on behalf of neurotoxin breakdown and elimination that can last for as many hours as the 36-hour half life of the anesthetic itself [30]. This process is part of inherent mechanisms of survival, regardless the neurotoxic, and it is automatically geared to protect the brain with interleukin-1 β (IL-1 β), and interleukin-6 (IL-6) pleiotropic mechanisms [6, 35–37].

This is significant considering the fact that, in the Netherlands alone, more than 32,000 killed patients have reportedly also died in conditions of unconsciousness with profound dehydration; and where, at least one pro-euthanization physician promoted the killing of a schizophrenic mentally ill patient to a general public readership with significant reference to the patient's ethnicity and immigrant socioeconomic demeaning reference to drug-addiction [38]. In this chapter, it is particularly relevant to disclose the fact that dementia patients can be proven to be inappropriate for euthanization treatment, both on the basis of their majority high-level of anti-somnogenic cytokine levels and on the basis of brain survival mechanisms that are successful enough to preserve the brain in the oldest dementia-symptomatic victims.

Generally speaking, anesthetics bind to gamma-aminobutyric acid (GABA) A subtype receptors of the central nervous system, the post-synaptic NMDA receptors of hippocampal pathways for memory, and the two-pore-domain K⁺ channels of the central nervous system, depressing signal transmission associated with conscious awareness for a surgical period. Extreme intravenous euthanatic administration does not reach the brain, according to manufacturer related research and instead produces risk of organ-wide tissue damage plus gangrene [30]. This is because the higher dosages trigger instant release of the pro-inflammatory cytokines tumor necrosis factor α (TNF α), interleukin-1 β (IL-1 β), and interleukin-6 (IL-6) which are powerful repair and survival brain protective cytokines [39, 40].

These cytokines modulate centers of wakefulness regulation located in the hypothalamus, the basal forebrain and the brain stem by influencing substances involved in sleep–wake-behavior such as adenosine, nitric oxide (NO), nuclear factor- κ B (NF- κ B), prostaglandin D2 (PGD2), the neurotransmitters γ -aminobutyric acid (GABA), glutamate and norepinephrine, as well as hormones such as growth hormone-releasing hormone (GHRH) and corticotropin-releasing hormone (CRH). However, several key cytokines including IL-4, IL-13 and TGF- β are anti-somnogenic (wakefulness triggering) [41]. If so, queries against forced euthanization of Alzheimer's disease should include high-risk of patient awakening susceptibility during the process, resulting in opportunity for greater error and patient suffering (see **Figure 1** below).

At the time of researching, Dutch physicians reportedly still seem to choose to administer pentobarbital at 9 g/L as the primary euthanatic, which is well above the 0.5 mg/L safe maximum (see online pharmaceutical manufacturing warnings [42, 43]. 71% of patients, dementia and non-dementia, are euthanised at home [30]. Methods of testing brain death and pain detection still include the Bispectral Index monitor (BIS), NeuroSense monitor and Analgesia Nociception Index monitor. There are evidence of pain and suffering, awakening, and discomfort during the euthanization, despite that it is promoted as a dignified pain-free method of termination from irreversible disease conditions [44].

And yet, the law refers to the patient's advance request to receive euthanization on behalf of preserving self-dignity which is separated from medical decisionmaking in itself. If so, there is an unchecked expression that could be interpreted as a mandate to destroy dementia-patients who visibly fail to prevent their symptoms from violating rules of local social dignity. If so, then this contradicts the claim of compassionate reasons for euthanization in the law-making.

In this chapter, a description is given of both. It includes:

- I.Measurement of decisionmaking decline in brain-disease related dementia;
and,
- II.Measurement of conscious-state transition impairment, and capacity to
accommodate euthanatic administration.

2. Measurement of decision-making decline in brain-disease related dementia

Decision-making decline in dementia patients [45] can be measured by using tests for autonomic non-conscious learning and recall expression [46]. The rates of learning and recall are measured from responses to an unconditioned stimulus (US) that is associated with a subsequent aversive conditioned stimulus (CS) [47]. Tests are described abundantly throughout the literature as the basis of cognitive *decisionmaking* [48–50] *evaluation*. The results are matched with the arrival of short-term neurosynaptic plasticity changes in corresponding neocortical amygdaloid-hippocampal-prefrontal cortical networks [51], as demonstrated by fMRI images offered in the Human Connectome Project (HCP) database [52, 53], relative to the disease etiology. XR-investigations are appropriate before stages of profound delirium in advanced dementia [54]. Delirium is defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) to include acute disturbance in attention, awareness, and cognition. The European Delirium Association and American Delirium Society (2014) describe its increased mortality rate [55]. Delirious patients suffer from severe disturbances of the circadian system [56]. And so, XR sessions as described in this chapter offer a diurnal monitoring method to predict the arrival of impaired day-night rhythm in patient dementia-related disease progression, long before stages of delirium have arrived.

Portable virtual reality devices that can simulate 360-degrees of 3D- immersive environments in videogame processing have been used in cognitive decision-making diagnostics and therapeutics. They can be scripted with internally-animated virtual cameras and objects, known as *assets* to trigger patient sensorimotor interaction and focus. The engagement parlays into recognition behaviors which can be recorded as data with simultaneous autonomic cardiologic variation measurements as frequently as needed in devices that stream the videogame up to 60 or more frames a second. Also known as serious games or medical virtual reality behavioral tests [54, 57], these videogames require a minimum set of calibration so that the collection of data from the patient (also referred to as the *player*) is medical-meaningful in investigations of decision-making decline and more.

For example, these include psychiatric considerations for:

- 1.Duration of each session which is minimized to avoid optogenetic influence on the patient bioreceptive retinal cells;
- 2.Diurnal (circadian) times of day that can report challenges due to brain inflammation transition stages, i.e. from inflammatory repair periods during the night to inflammatory protection during the day;
- 3.Patient locomotor stabilization and non-navigational requirements against disorientation and injury;

4. Bioperceptive capacity versus retinal limitations that reduce visual motion-detection and circadian synchronization;
5. Headturning rates, restrictions and sensorimotor ease;
6. Heart-rate variation monitoring that is reliable throughout each XR-test session;
7. Saccadic “blink” synchronization with behavioral sampling;
8. Real-world time of day consistency of the XR-session for both scotopic and photopic illumination intensity calibrations;
9. Statistical evenness in game scenes without the use of biased cultural asset-objects in the environment;
10. Geotimestamped coordinates of player position and any testing-related assets and events;
11. Alignment of player data with existing patient psychiatric evaluations and clinical epidemiological research; plus,
12. Appropriate asset-labeling, tagging, data-reporting standards and patient privacy integrations.

The reader is encouraged to review a detailed description of how these features may be presented in a Supplementary Materials section titled, *Example XR-setup for Decision-making Decline Monitoring of Dementia Patients*.

3. Measurement of conscious-state transition capacity under euthanatic administration

The thalamocortical pathway is central to cortical network information processing during conscious-state transition behavior [58] including auditory and visual sensory information response with emotion-based learning and recall networks. It is influenced by bioperception related retinal vibrations received via the suprachiasmatic nucleus and retinohypothalamic tract, along with influence from genetic signaling (e.g., CLOCK, BMAL1 and others) governing overall homeostasis [59–61]. The networks include the primary and secondary association area networks of the brain neocortex, as well as networks involving the orbitomedial prefrontal cortex (OMPC, areas 11 & 12) as part of the region described by the limbic cortex and septal nuclei (including the amygdala) on behalf of patient mood regulation monitoring, the hippocampus, the thalamus and basal ganglia which are directly involved in sleep/wake environmental awareness-states [62]. The disruption of these networks occurs from circadian desynchronization and the persistence of neuroinflammation [63]. Images of such disruption and the resulting network changes from neurodegeneration can be seen in detail from fMRI image repositories provided by the Human Connectome Project [52], the Alzheimer’s Disease Connectome [64], and similar collections. In fact, a future generation Connectome project might include the complementary circadian-calibrated XR-based data collected from dementia patients across multiple demographics, for key times of day, pre-dawn, mid-day and pre-dusk to dusk. A schematic for a

potential model of selected networks with the Human Connectome is shown in **Figure 2**, below.

Currently, no tool exists to measure consciousness or self-consciousness objectively by any machine [65]. In non-communicative patients, its estimation requires the interpretation of motor responsiveness [66]. This response represents active brain processing events in the Primary Motor Cortex (MI, area 4) in the precentral gyrus and the corticospinal tract which has its own relationship to somatotopic organization for specific movement coordination, in general with other sensory processing information via a major thalamic motor nucleus, including its ventral

Figure 2. Schematic example of a selected nucleic-network XR model using the human connectome project (HCP). HCP hosts detailed neuromorphological fMRI datasets combining networks from dementia and related human and animal pathology treatment records. An assembly of virtual reality (XR) monitoring programmes can be organized to support integration with HCP data collections for dementia patients, focusing on any range of selected neuronal-nucleic networks.

lateral nucleus (VL) and Ventral anterior nucleus (VA), and in the presence of dementia-related inflammation [67, 68].

In the Supplementary Materials, a list of some of the parameters are explained so that optogenetic waveform signals are consistent within the virtual reality scene as they are in the natural environment that activates synaptic relays between the intralaminar nucleus of the thalamus and the sensory-information processing cortical networks. These are the same brain regions associated with awareness of self, in relationship to the environment.

Testing in XR can be used to evaluate the degree of this circadian desynchronization in dementia patients, as long as photopic and scotopic illumination settings are maintained for real-world time-of-day concurrently. γ -Amino-Butyric-Acid (GABA) is necessary for refinement of the circadian firing rhythm that maintains healthy conscious-state transition processes throughout every brain region via the suprachiasmatic nucleus [69] and connecting intergeniculate leaflet (IGL) and retinohypothalamic tract to thalamocortical and related nuclei (**Figure 3**) is responsible for healthy circadian integration of environmental-information throughout multiple cellular oscillations [13] in observable brainwaves.

Circadian daylight regulation [70] via the suprachiasmatic nucleus is also crucial to the production of anti-inflammatory melatonin and so, it would be questionable to find XR-circadian related prosthetics lacking in palliative care for dementia patients.

Melatonin, secreted by the pineal gland, protects neuronal cells with its antioxidant and anti-amyloid properties, and helps to limit or reduce formation of amyloid fibrils involved in Alzheimer-like tau hyperphosphorylation [71, 72]. In neuroinflammatory dementia patients, phase shifts of daylight into dusk trigger agitation, aggression, and delirium during the late afternoon and early evening hours [73], a behavioral regulatory challenge known as *sundowning* [74]. Medically, it is vital to incorporate this condition as a risk of additional suffering during euthanization administration, particularly where euthanatic neurotoxic delivery does not reach the brain and the patient is already conscious-state transition severely impaired (see **Figure 4**).

The XR-tests in conscious-state transition offer an opportunity to evaluate retinal-support as part of psychiatric comfort targets [75] or, to evaluate potential pharmaceutical risk of overdosing a dementia patients.

Figure 3.
A simplistic schematic of the bioperception circadian excitatory (yellow) and inhibitory (green) response neuronal-nucleic network relationships, for XR-calibration development purposes.

Figure 4.
Relationship of melatonin absence and elevated risk of dementia alert/awake or risk of convulsion.

4. Summary

In this chapter, an XR-based method for evaluating decision-making competence is presented. In reaction to a recent Dutch law that suggests decision-making incompetence is sufficient grounds for non-voluntary euthanization of dementia patients. Instead, this chapter proposes that decision-making needs to be measured precisely along with conscious-state transition using XR. This is because majority of dementia patients cannot transition from alert or rest state to death state instantly, and that this predisposes them to high risk of brain aware and awake state, including for the duration of the euthanatic product half-life, and despite cardiac arrest. And so, the Dutch law which currently only describes patient-disease irreversibility and social dignity loss, appears to overlook the need to evaluate disease conditions and patient conditions for which euthanization is not medically safe and non-voluntary euthanization of such patients is cruelty.

XR-based tests are described as short-instance virtual environmentally-interactive tests, provided in diurnal sessions that have been calibrated to the circadian optogenetic settings of neuronal-nucleic brain thalamocortical networks. The tests provide opportunity to demonstrate neuroinflammation progression and the impact of high expression of anti-somnogenic cytokines, the loss of anti-inflammatory neuroprotective melatonin and circadian desynchronization to the patient. This makes XR-based monitoring in palliative patient caregiving generally valuable as well as key to evaluation of euthanization-readiness.

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A. Appendix

A.1 Example XR-setup for decision-making decline monitoring of dementia patients

A.1.1 XR-scene development technology

Any state-of-the-art software can be used for dementia-related testing, such as Unity3D®, Unreal®, which are designed for maximum accessibility and ease-of-development for diverse developers. They lack psychiatric calibration and features suited to patient cognitive behavioral environmental-interactive capture and heartrate AI, as well as geographic solar-shadow and weather calibration for both illumination intensity draws and audio. Last but certainly not least, the player analytics do not accommodate sampling frequencies and these will need to be hand-built, which leads to significant reduction in frame rates at the time of this chapter's writing. For this reason data needs to be stored on the device for post-session upload and integration into an appropriate repository. In general, leading palliative care institutions should try to achieve approximately 600 longitudinal sessions per patient for at least 1200 patients⁵⁶ to generate a suitable diagnostic game AI algorithm [57]. These totals represent average numbers of records submitted to the previously-mentioned Human Connectome Project, for example.

Ethical consideration: Large commercial database hosting sellers are eager to acquire patient data for free. And yet, healthcare costs of the producer, the dementia patient, and the time and technology costs are abandoned or ignored. A fee per interaction should be required from the sellers per frame, and reimbursed towards the patient's full needs, particularly those patients and teams who seek rehabilitation strategies and research for immediate potential curative-care opportunities with XR-related prosthetics.

The simplest platform or device that is VR-enabled and lightweight for hosting a real-time XR-scene for a stationary player is suitable. This can include a basic phone such as a Samsung(R) 10 or 10+ in a Gear VR headset, or an Oculus Rift product, and similar. The ideal software will include AI-calibrated illumination intensity and unbiased wavelength delivery, from a light-emitting diode (such as an AMOLED strip) plus brightness settings that can be adjusted manually by the team. It will also collect geographic coordinates of the player, plus time-of-day and ambient light, pollution and player Fowler's position, heartrate plus saccadic blinking and eye-tracking. The data collected may need to be temporarily stored on the device and so it should also have sufficient hardware capacity both to allow non-occluding GPU rendering and device storage for a 3-minute game processing and behavioral sampling every 30 seconds, minimum at a framerate no less than 32 to 45 frames per second. In a headset, ensure that audio settings conform to any hearing aid or other

prescription settings. The same is true for visual aid adjustments in the VR-headset. Handheld peripherals should not be used or required for dementia autonomic cognitive decision-making and conscious-state transition settings. The patient should not be required to navigate at any time and a member of the diagnostic patient caregiving team is responsible for the condition, use and removal of the XR-assembly from the patient in all sessions.

A.1.2 Significant parameters

Waveform calibration parameters describe phototopic and scotopic settings.

A.1.3 Scene environments

Testing environments for adult-onset dementia-related patients should not be designed to evaluate decisions based on visible timer scoring, navigation decisions through civil-type architecture or semantic response requirements. These do not represent measure states of neuroinflammation-affected decision-making, based on short-term learning and recall.

Sky and ground assets above the horizon should be reported in the asset-inventory as either left and right orientable.

Parameters that describe the maximum spread of the wavelength field such as fulcrum depth and width can also be used to evaluate conscious-state transition where there are compounding or ageing related deficits in one or both hemispheres. These parameters describe the geometric projection of the user's virtual camera-space and orientation of the player's head rotation and line of direction in the virtual scene.

The raycast direction is the parameter used in scripts of assets to report the player's line of direction. The raycast direction describes direction of focus, and is key to describing a change in patient conscious-state. The rate of change of raycast direction is used in behavioral response measurements in recognition and recall of an asset during a nonconscious test.

A.1.4 Light wavelength calibration

Wavelength intensity can be given for assets in parameters from all assets, including sky and ground, vegetation, weather and wildlife. The parameters can be described as 0-1 transparency alpha, depth projection, non-spectral shading component size, reflective source component size, rate of single-asset motion (blur), landscape contrast intensity (sharpness), and scene illumination intensity, whichever is appropriate and convenient to describing striking behavioral response differences.

The most critical wavelengths are blue: 450–485 nm 620–680 THz 2.64–2.75 eV and red: 625–740 nm 405–480 THz 1.65–2.00 eV on behalf of impact to hippocampal neuronal, and genetic signaling targets involved in transcription/translation feedback loop of CLOCK and BMAL1, and the nucleus basalis magnocellularis projections to the suprachiasmatic nucleus (SCN) mentioned in the main chapter text and shown in **Figure 3**. Cone and melanopsin signaling determines brightness perception. There are references available which suggest that melanopsin excitation takes place at brightness equal to $1 \text{ cd} \cdot \text{m}^2$ for an equal-energy-spectrum light at $1 \text{ cd} \cdot \text{m}^2$. The maximum range should lie within 380–780 nm, which represents the range of skylight visible to human bioperception from pre-dawn to post-dusk.

A.1.5 Retinal luminance

Luminance is in the research to have a defined photon catch of around 480 nm of opsin.

For this reason, maximum error in the device rendering of luminance should be no more than 10% from this value based on maintaining exactly 480 nm spectrally per session.

Mobile device platform manufacturers have responded to health-risk concerns in reported from excess levels of LED blue-light exposure [76]. On the other hand, the research suggests improvements to these same conditions [77, 78]. For these reasons, timing and duration of a virtual reality monitoring session should be coordinated to start at the first eye-blink, and no longer than three (3) minutes. In fact, the first sampling of sensori-motor response and heart rate should be at the instance of the first patient saccadic (blink). This ensures coordination of the data collection with the timing of innate cognitive recognition such as orientation or focus and dorsomedial prefrontal cortex response signaling. It includes the arrival of a new spatial learning event in the hippocampal brain region.

A.1.6 Event rendering

For sky this can also include stimulatory parameters that increase the decision-making integrity challenge, including parameters such as: sky-to-ground relative volume and types of event, such as fog-cloud-rain particle settings. Similarly, parameters for ground can include: ground illumination intensity, ground volume

and vegetation-variation, vegetation-windspeed events and so on. Keep in mind that virtual reality involving scores and changing scenes can trigger psychological discomfort, dizziness, eye-strain and even addiction [79–81]. For this reason, there should be only one scene with nature-related motion such as wind in grass or tree branch swaying, and water ripples rather than ground buoyancy.

A.1.7 3D-Audio

Audio settings are vital to immersive realism but, may be varied on left and right, such as for early dementia-related auditory-thalamocortical peri-operative risk evaluation or for patient prescription purposes. Manufacturer settings usually offer sufficient audio control parameters.

A.1.8 Scene bias

No civil society structures, roads, signs whether semantic or drawings, volume-measurement, clock-measurement or human relationship and non-nature type cue references should be included in neurobehavioral XR-testing that is intended to predict the condition of neuronal-nucleic cellular health or tissue functioning.

A.1.9 Behavioral sampling

Thirty second sampling intervals to collect the sensorimotor response and heartrate variation represents successive periods for potential long-term synaptic potentiation in the patient, such as would belong to a learning or decision event based and with matching cerebroarterial blood flow occurring in potential simultaneous XR-fMRI BOLD patient observation. Since daylight variations is composed of wavelengths of light whose frequency and phase change with the position of the sun, it is important to sample for all significant periods of the day in which daylight variation is significant, i.e. the behavioral response from pre-dawn all the way to post-dusk in 3 minute intervals for minimum of 5 or 6 XR-testing sessions, as shown in the sampling tables, below. During an XR-session, wavelight phase information stimulates the retinal cells depending on the device illumination levels (sometimes referred to as *Troland* units, representing retinal illumination from 1mm^2 pupil area exposed to $1\text{cd}/\text{m}^2$ (candelas/ m^2) of scene light). Light information is translated vibromechanically by the photosensitive retinal ganglion cells onto the suprachiasmatic nuclei cells which directly stimulate the hippocampal neural bed for short-term neuronal growth. The process relies on intracellular transport via light-sensitive heterodimerization which recruits specific proteins in hippocampal neurons, involving recycling endosomes on behalf of neuron axon outgrowth [82]. If XR is used as a circadian prosthetic, this information can be helpful to measuring the amount or volume of full daylight needed for restoring circadian synchronization, using known optogenetic principles of cellular mitochondrial activation and targets in the retinohypothalamic and limbic region circuitry [83].

During a single test event an unconditional stimuli (US) is followed by an unknown conditional stimulus (CS) to the patient, as described in the chapter. This can be for example, a sudden thunder event in a random location that follows the appearance of a bird. The response to the stimuli should be reasonable but significant enough to trigger a cognitive autonomic learning process in healthy controls so that the response behavior is repeated at the next appearance of the same bird, even if the thunder does not occur. In this process, nonconscious autonomic decisionmaking behaviour can be recorded by any XR-scripts that report the raycast change of direction associated with the patient's change of focus and change of heartrate. In Alzheimer's Disease related dementia, for example, there would a

noticeable delay in heartrate variation at the time of change of raycast direction. In mid-day testing, learning and recall decisionmaking might appear to be significantly greater than in dusk-based sessions for a wide variety of dementia related diseases. This is because the pathway between the photosensitive retinoganglion cells to the thalamocortical nuclei may be compromised by the disease, such that the hippocampal cells via the retinohypothalamic tract do not receive sufficient day-light phase management information. The loss of daylight wavelength variation from pre-dawn to post-dusk impairs conscious-state transition and increases patient confusion and risk of sleep disruption and hallucination.

A.2 Examples of XR-data-collection setup

Session: Control Mid-day (photopic scene): Patient device optimization check Heart rate streaming check. This requires checking the asset acoustic and animation visibility for distant, near, left and right positions, plus in sky and on ground) Note: Patient is standing or seated and stationary at all times. Distant: <20,000m virtual radius Near: <1000m virtual radius											
Nonconscious-asset Type: None Animation Type: None	Start										End
Sampling interval:	00:00:00	00:00:30	00:00:60	00:01:05	00:01:10	00:01:30	00:02:00	00:02:05	00:02:00	02:30	03:00
Heart rate variation											
Sensorimotor response rate-left											
Sensorimotor response rate-right											
Sky Contrast ratio-left	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Sky Contrast ratio-right	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Contrast Sky-Ground	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Rate of conscious-state transition response											
Total Cognitive Responsiveness											
Total Decision-variation											
Session: Pre-dawn (photopic scene): Nonconscious asset is animated on the ground level, in a distant, near, left or right start position Note: Patient is standing or seated and stationary at all times. Note: Patient is standing or seated and stationary at all times. Distant: <20,000m virtual radius Near: <1000m virtual radius											
Nonconscious-asset Type: Visual and Auditory Animation Type: Approaching	Start (blink)			US left	CS left				US left		End

Sampling times	00:00:00	00:00:30	00:00:60	00:01:05	00:01:10	00:01:30	00:02:00	00:02:30	00:02:32	02:34	03:00
Heart rate											
Sensorimotor response rate-left											
Sensorimotor response rate-right											
Sky Contrast ratio-left	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Sky Contrast ratio-right	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Contrast Sky-to-Ground	0.3	0.3	0.3	0.8	0.8	0.3	0.3	0.8	0.3	0.3	0.3
Rate of conscious-state transition response											
Total Cognitive Responsiveness											
Total Decision-variation											

Example Pre- to Post-Dawn Interval: 20-50 minute

Session: Post-dawn (photopic scene) Ground-level asset-test Nonconscious asset is animated on the ground level, in a distant, near, left or right start position. Note: Patient is standing or seated and stationary at all times. Distant: <20,000m virtual radius Near: <1000m virtual radius											
Nonconscious-asset Type: Visual and Auditory Animation Type: Approaching	Start (blink)			US left	CS right				US left		End
Sampling times	00:00:00	00:00:30	00:00:60	00:01:05	00:01:10	00:01:30	00:02:00	00:02:30	00:02:32	02:34	03:00
Heart rate											
Sensorimotor response rate-left											
Sensorimotor response rate-right											
Sky Contrast ratio-left	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Sky Contrast ratio-right	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Contrast Sky-to-Ground	0.3	0.3	0.3	0.8	0.8	0.3	0.4	0.8	0.4	0.4	0.4
Rate of conscious-state transition response											
Total Cognitive Responsiveness											
Total Decision-variation											

Example Post-Dawn to Mid-day Interval: 4 hours											
Session: Mid-day (no shadow) (photopic scene) Nonconscious asset is animated on the sky level, in a distant, near, left or right start position Note: Patient is standing or seated and stationary at all times. Distant: <20,000m virtual radius Near: <1000m virtual radius Luminance (log cd/m2): 4 to 6 Pupil diameter (mm): 6 to 8 Retinal illuminance (log Trolands): Photopic > 4.5 /Scotopic 0 Active photoreceptors: cones Color perception/acuity: Good color vision, high acuity											
Nonconscious-asset Type: Visual and Auditory Animation Type: Approaching	Start (blink)			US left	CS left or right				US left		End
Sampling times	00:00:00	00:00:30	00:00:60	00:01:05	00:01:10	00:01:30	00:02:00	00:02:30	00:02:32	02:34	03:00
Heart rate											
Sensorimotor response rate-left											
Sensorimotor response rate-right											
Sky Contrast ratio-left	0.5	0.5	0.5	0.8	0.8	0.5	0.5	0.5	0.8	0.5	0.5
Sky Contrast ratio-right	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Contrast Sky-to-Ground	0.4	0.4	0.4	0.4	0.4	0.5	0.5	0.5	0.5	0.5	0.5
Rate of conscious-state transition response											
Total Cognitive Responsiveness											
Total Decision-variation											
Example Mid-day to Pre-dusk Interval: 6 - 8 hours											
Session: Pre-dusk (photopic scene) Nonconscious asset is animated on the sky or ground level, in a near left or right start position Note: Patient is standing or seated and stationary at all times. Near: <1000m virtual radius											
Nonconscious-asset Type: Visual and Auditory Animation Type: Approaching	Start (blink)			US left	CS left				US left		End
Sampling times	00:00:00	00:00:30	00:00:60	00:01:05	00:01:10	00:01:30	00:02:00	00:02:30	00:02:32	02:34	03:00
Heart rate											
Sensorimotor response rate-left											
Sensorimotor response rate-right											

Sky Contrast ratio-left	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Sky Contrast ratio-right	0.5	0.5	0.5	0.8	0.5	0.5	0.5	0.5	0.8	0.5	0.5
Contrast Sky-Ground	0.3	0.3	0.3	0.3	0.8	0.3	0.3	0.3	0.3	0.3	0.3
Rate of conscious-state transition response											
Total Cognitive Responsiveness											
Total Decision-variation											

Example Pre-Dusk to Post-Dusk Interval: 20-50 minutes

Session: Post-dusk (photopic scene)
Nonconscious asset is animated on the ground level, in a near left or right start position
Note: Patient is standing or seated and stationary at all times.
Near: <1000m virtual radius

Nonconscious-asset Type: Visual and Auditory Animation Type: Approaching	Start (blink)			US random	CS left				US random		End
Sampling times	00:00:00	00:00:30	00:00:60	00:01:05	00:01:10	00:01:30	00:02:00	00:02:30	00:02:32	02:34	03:00
Heart rate											
Sensorimotor response rate-left											
Sensorimotor response rate-right											
Sky Contrast ratio-left	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Sky Contrast ratio-right	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Contrast Sky-to-Ground	0.2	0.2	0.2	0.8	0.8	0.2	0.2	0.2	0.8	0.2	0.2
Rate of conscious-state transition response											
Total Cognitive Responsiveness											
Total Decision-variation											

Session: Post-dusk (photopic scene)
Nonconscious asset is animated on the ground level in a near, left or right start position
Note: Patient is standing or seated and stationary at all times.
Near: <1000m virtual radius

Nonconscious-asset Type: Visual and Auditory Animation Type: approaching	Start (blink)			US random	CS right				US random		End
Sampling times	00:00:00	00:00:30	00:00:60	00:01:05	00:01:10	00:01:30	00:02:00	00:02:30	00:02:32	02:34	03:00
Heart rate											

Sensorimotor response rate-left											
Sensorimotor response rate-right											
Sky Contrast ratio-left	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Sky Contrast ratio-right	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Contrast Sky-to-Ground	0.2	0.2	0.2	0.8	0.8	0.2	0.2	0.2	0.8	0.2	0.2
Rate of conscious-state transition response											
Total Cognitive Responsiveness											
Total Decision-variation											

Session: Post-dusk (starry-night scatter) (photopic scene) Nonconscious asset is auditory in the sky or ground level, in a distant, near, left or right start position Note: Patient is standing or seated and stationary at all times. Distant: <20,000m virtual radius Near: <1000m virtual radius Luminance (log cd/m2): -6 to -4 Pupil diameter (mm): 7.1 to 6.6 Retinal illuminance (log Trolands): Photopic < -0.62 /Scotopic -4.0 to 0.70 Active photoreceptors: rods Color perception/acuity: No color vision, poor acuity											
Nonconscious-asset Type: Auditory Animation Type:None	Start (blink)			US random				UC random			End
Sampling times	00:00:00	00:00:30	00:00:60	00:01:05	00:01:10	00:01:30	00:02:00	00:02:05	00:02:00	02:30	03:00
Heart rate											
Sensorimotor response rate-left											
Sensorimotor response rate-right											
Sky Contrast ratio-left	0	0	0	0	0	0	0	0	0	0	0
Sky Contrast ratio-right	0	0	0	0	0	0	0	0	0	0	0
Contrast Sky-to-Ground	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Rate of conscious-state transition response											
Total Cognitive Responsiveness											
Total Decision-variation											

Repeat the above, for Scotopic settings and report.
Compare and analyse daily mid-day decision-variation longitudinal data.
Refer to rate of loss of conscious-state transition as:
Behavioral range > 0

Heartrate variation (time of US event recognition) = Heartrate variation (recall of CS event)

And

Headturn rate or focus > 0 and raycast-direction collides with the CS event location of asset

```
function Update () {
  var hit : RaycastHit;
  if(Physics.Raycast(transform.position, transform.up, hit, 10))
  {
    contact = true;
  }
  else
  {
    contact = false;
  }
}
```

change to a US-trigger (based on change of raycast direction and speed) relative to patient heartrate variation, for dusk versus mid-day and dawn versus mid-day behavioral responses.

In general, this could verily indicate a medically-prohibitive gradient for euthanatic administration.

A.3 Additional evidence-seeking requirements recommended prior to non-voluntary patient killing including physician account investigation

Behavioural Impairment	<ul style="list-style-type: none">Virtual Reality-fMRI/PET ModelsFocus on models of the prefrontal-amygdala circuits and Amygdalo-Prefronto-Dorsostriatal Network reaction timesInclude autonomic pavlovian fear-conditioning variations : differences in cerebrovascular response times versus and cardiovascular.
Pain and Suffering	<ul style="list-style-type: none">Include stress-related wipe-out (losses) of immunity-providing gut, blood and genital microbiota (e.g., Lactobacillus, in conversion of tryptophan to kynurenine for neurotransmitter synthesis and neuroinflammation regulation).Look for increased GI tract permeability and alterations to the neurohumoral communication along the vagus nerve and enteric nervous system, and HPA axis activationMeasure the patient inflammation leading to infection and psychological impairments
Infection and Organ Damage	<ul style="list-style-type: none">Look for records of Increased GI tract permeability and inflammation leading to infection and psychological impairmentsInclude pharmaceutical induced evidence of Circadian disruption, sleep-interruptionUse medical diagnosis (or absense thereof) to report potential psychiatric neglect of loss of neuronal - and inflammatory repair rates, leading to cognitive disruption, and suicidal drive.
Physical Weakness & Exhaustion	<ul style="list-style-type: none">Compare patient decline with models of post-traumatic stress disorder patientsTarget the increased sympathetic tone and decreased parasympathetic activity activation of the stress response and central and peripheral immune cellsRequest patient records where physicians failed to examine cardiovascular reactivity and to monitor early signs of onset cardiovascular disease (CVD)

These represent brain neurotoxic inflammatory evidence that are treatable and curable. When these features are collectively neglected, the patient becomes more dependent on support and may be at higher risk of a non-voluntary commitment to his/her death by physicians or psychiatrists who have not conducted a proper full assessment for a minimum of three months.

A.4 Nervous system relationships for autonomic and conscious behavioral response regulation

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