Arousal and Regulatory Systems: Workshop Proceedings

June 24-26, 2012
Rockville, MD

Background

The Research Domain Criteria (RDoC) project is designed to implement Strategy 1.4 of the NIMH Strategic Plan: *Develop, for research purposes, new ways of classifying mental disorders based on dimensions of observable behavior and neurobiological measures.* NIMH intends RDoC to serve as a research framework encouraging new approaches to research on mental disorders, in which fundamental dimensions that cut across traditional disorder categories are used as the basis for grouping patients in clinical studies. RDoC represents an inherently translational approach, considering psychopathology in terms of dysregulation and dysfunction in fundamental aspects of behavior as established through basic neuroscience and behavioral science research. The major RDoC framework consists of a matrix where the rows represent specified functional *Constructs*, summarizing data about a specified functional dimension of behavior, characterized in aggregate by the genes, molecules, circuits, etc., responsible for it. Constructs are in turn grouped into higher-level *Domains of functioning*, reflecting contemporary knowledge about major systems of cognition, motivation, and social behavior. In its present form, there are five Domains in the RDoC matrix: Negative Valence Systems, Positive Valence Systems, Cognitive Systems, Systems for Social Processes, and Arousal/Regulatory Systems. The matrix columns specify *Units of Analysis* used to study the Constructs, and include genes, molecules, cells, circuits, physiology (e.g., heart-rate or event-related potentials), behavior, and self-reports. The matrix also has a separate column to specify well-validated paradigms used in studying each Construct.

The RDoC matrix is being developed to serve as a heuristic and it is subject to change with scientific advances from the field. To "build the matrix," NIMH has been bringing together leading experts to coalesce and articulate the state of knowledge for each of the five domains. Six meetings are planned: this workshop, focused on the Arousal and Regulatory Systems domain, was the sixth in the series.

For detailed information about RDoC, proceedings from prior workshops, and the updated matrix, please see the RDoC web page.

Workshop Proceedings

The NIMH RDoC Working Group initially proposed three draft Constructs within the Arousal and Regulatory domain: 1) Arousal, 2) Biological Rhythms, and 3) Default Readiness. Based on each individual's scientific expertise, the workshop participants were assigned to one of three "construct groups". Each group was tasked with 1) deciding whether and how their group's Construct(s) should be revised from the original conceptualization, 2) generating a definition for each Construct, 3) filling in the elements of the matrix for each Unit of Analysis for the Construct(s) and 4) generating a list of promising and reliable research paradigms that can be

used to study the Constructs. The construct groups were split into two parallel breakout groups, each with their own moderator, to facilitate discussion and encourage exploration of divergent opinions (with the exception of the Biological Rhythms group, which functioned as one large group). Following breakout group meetings, the construct groups reassembled for further discussion and refinement of the products, which was followed by an iterative process of reporting-out and discussion with the entire workshop and reconvening in construct groups.

The workshop participants discussed the RDoC team's proposed constructs and suggested some re-organization and re-naming. In addition to discussing and refining the constructs proposed by the RDoC working group, the workshop participants reached consensus on the addition of a fourth construct, Sleep and Wakefulness, and generated a definition and a matrix for this construct also. The group that was assigned to the Biological Rhythms construct modified the construct to be Circadian Rhythms. These definitions and summaries of the groups' discussions are provided below.

The Default Readiness group revised the construct to be the Default Mode Network (DMN). The group members discussed at length whether DMN met the criteria for an RDoC construct, and developed a definition and matrix elements despite this uncertainty. Ultimately, however, the NIMH RDoC working group decided that DMN was not appropriate for inclusion as a construct because of the lack of specificity of the DMN among intrinsic neural networks and the ambiguous link to behavior and psychopathology. The preliminary Construct definitions, the summary of the workshop group's deliberations, and the matrix for DMN are in a separate section below.

Construct Definitions

1. Arousal: Arousal is a continuum of sensitivity of the organism to stimuli, both external and internal.

Arousal:

a) facilitates interaction with the environment in a context-specific manner (e.g., under conditions of threat, some stimuli must be ignored while sensitivity to and responses to others is enhanced, as exemplified in the startle reflex);
b) can be evoked by either external/environmental stimuli or internal stimuli (e.g., emotions and cognition);
c) can be modulated by the physical characteristics and motivational significance of stimuli;
d) varies along a continuum that can be quantified in any behavioral state, including wakefulness and low-arousal states such as sleep, anesthesia, and coma;
e) is distinct from motivation and valence, but can covary with intensity of motivation and valence;
f) may be associated with increased or decreased locomotor activity; and,
g) can be regulated by homeostatic drives (e.g., hunger, sleep, thirst, sex).

2. Circadian Rhythms: Circadian rhythms are endogenous, self-sustaining oscillations that organize the timing of biological systems to optimize physiology, behavior, and health.

Circadian Rhythms:

a) are synchronized by recurring environmental cues;
b) anticipate the external environment;
c) allow effective responses to challenges and opportunities in the physical and social environment;
d) modulate homeostasis within the brain and other (central/peripheral) systems, tissues, and organs; and,
e) are evident across levels of organization including molecules, cells, circuits, systems, organisms, and social systems.

3. Sleep and wakefulness: Sleep and wakefulness are endogenous, recurring, behavioral states that reflect coordinated changes in the dynamic functional organization of the brain and that optimize physiology, behavior, and health. Homeostatic and circadian processes regulate the propensity for wakefulness and sleep.

Sleep:

a. is reversible, typically characterized by postural recumbence, behavioral quiescence, and reduced responsiveness;
b. has a complex architecture with predictable cycling of non-rapid eye movement /rapid eye movement (NREM/REM) states or their developmental equivalents; NREM and REM sleep have distinct neural substrates (circuitry, transmitters, modulators) and EEG oscillatory properties;
c. intensity and duration is affected by homeostatic regulation;
d. is affected by experiences during wakefulness;
e. is evident at cellular, circuit, and system levels; and,
f. has restorative and transformative effects that optimize neurobehavioral functions during wakefulness.

SUMMARY OF CONSTRUCT GROUP DELIBERATIONS

The material in the following sections is intended to provide background and context for the final construct definitions as provided above. Workshop participants discussed a variety of considerations and perspectives, and the resulting set of constructs and their definitions emerged.

Arousal

Specificity versus ubiquity

The Arousal construct group first discussed how best to clarify arousal depending on the factors that might drive the arousal as distinguished by internal or external stimuli, and also depending on valence. For instance, in the case of valence, different circuits might be relevant to positive, negative, or neutral valence. There was also a lot of discussion about the potential need for specific sub-constructs, such as those related to stress, fear, sex, or feeding drive states. In other words, is the final common pathway of arousal sufficient to capture these different drive-states? One of the challenges is that recent thinking about arousal postulates diffuse but interrelated pathways that are connected, as compared to earlier ideas that held that arousal was driven largely in a singular fashion by the more primitive areas of the brain. During discussions with the larger group, it was noted that arousal systems, such as the noradrenergic system, when activated, have pervasive effects, as does the hypocretin system. However, there appears to be some evidence that there is specificity—for instance, activation of the hypocretin system in relation to positively reinforced, but not negatively reinforced behaviors. It was also noted that more specificity might come from the observation that various arousal systems (e.g., noradrenergic, serotonergic, histaminergic, cholinergic, glutamatergic) are not typically activated together. Thus, these systems could not only be differentially activated, but also be driven by (and drive) activation in different brain regions. There was the suggestion that more knowledge is needed on how these systems converge, act in concert, or exhibit specificity for driving activation in various brain regions, or for their relation to behaviors relevant for mental illness. In other words, is the final common pathway driven by very different systems? This discussion reflected a challenge that the Arousal-Regulatory group faced: that these systems are pervasive and operate throughout the entire brain.

Appetitive and aversive arousal

There was agreement that arousal is a continuing sensitivity of the organism to stimuli, both external and internal. It was also considered that distinct arousal-related neural circuitry can be activated under appetitive and aversive conditions, such as noradrenergic and dopaminergic neurons that can be assessed by the tonic discharge level of locus coeruleus neurons, and the amount of norepinephrine that is subsequently released. Other arousal systems may be activated under either appetitive or aversive conditions, controlling specific, affectively-neutral behaviors that are associated with the elevated arousal levels. All of these arousal systems may act differently under conditions of sleep or wakefulness. For example, activity in arousal-promoting circuits may act entirely differently during REM sleep versus NREM sleep and waking states; lengthening and intensifying the former, but promoting wakefulness and arousal in the latter.

That is, amygdala stimulation increases REM sleep length; loud noises (90 dB) that arouse during NREM sleep either increase the intensity of REM phasic events or increases the length of REM sleep.[1] Thus, the function of the circuits for arousal changes during REM sleep.

Arousal in relation to sleep and wakefulness

The Arousal group deliberated on how best to distinguish sleep-wakefulness from arousal. Following discussions within this construct group and with the members of the Circadian Rhythms construct group, there was consensus that arousal and sleep are indeed different constructs. Although arousal and sleep are often viewed on a single continuum, it was argued that this may be too simplistic, as individuals can have relatively higher and lower levels of arousal during sleep and during wakefulness. The neural circuitry that regulates sleep and wake states is well-described in animals and humans, overlapping with, but not identical to, that of arousal systems. Arousal is often considered to fluctuate momentarily in response to external or internal stimuli. Sleep and wakefulness, on the other hand, are regulated by interacting homeostatic and circadian processes with long time constants that may be influenced by, but are not identical to, momentary arousal. Sleep also demonstrates local use-dependency and local variations in intensity on cellular and circuit levels.

Sleep and wakefulness are clearly "dimensions of observable behavior and neurobiological measures." Moreover, they have great relevance to mental disorders: Disturbed sleep is one of the most common trans-diagnostic features of mental disorders; it is one of the most consistent risk factors for the development of subsequent mental disorders; it is associated with worse treatment outcome in a variety of disorders; and treating sleep disturbance may improve the outcome of mental disorders. Sleep and sleep disturbance also affect function in each of the other RDoC domains, including Negative Valence Systems, Positive Valence Systems, Cognitive Systems, and Systems for Social Processes. After deliberation within the construct group, it was decided that the Arousal group and the Circadian Rhythms group would work together to develop a definition and matrix for the Sleep-Wakefulness construct, and these deliberations are summarized under Sleep-Wakefulness below.

Matrix elements

This group identified a number of circuits and neurotransmitter systems that were relevant to arousal, which are included in the Matrix.

The group also discussed clinical conditions related to arousal including coma, psychopathy, post-traumatic stress disorder (PTSD), attention deficit/hyperactivity disorder (ADHD), depression, bipolar disorder, Alzheimer's disease, and psychosis.

Arousal paradigms were offered with the caveat that no single measure is applicable across the entire continuum or across all conditions.

Circadian Rhythms

The Circadian Rhythms (CR) construct group first decided that, while it was necessary to include body-brain interactions in circadian rhythms and reference to peripheral clocks in the constructs, these would be included only in so far as they had an impact on mental health. Though biological rhythms include circadian, ultradian, and seasonal oscillations, there is very little evidence to support the presence of ultradian or seasonal oscillations in the human mammal. Therefore, for the purpose of translational research relevant to mental health, CR is included as the sole entry at this time.

The initial definition put forward was that circadian rhythms are endogenous, self-sustaining oscillations that organize the timing of biological systems to optimize physiology, behavior, and health (by "behavior," the group included affect, valence, and cognition as defined in the other Constructs). Two important aspects of biological rhythms were highlighted: their self-sustaining, endogenous, character and their ability to anticipate and lead to a readiness to respond to events in natural settings.

The oscillatory nature of biological rhythms was considered important; however, the group decided to include only those oscillations with the greatest evidence to support a role in circadian rhythms, as defined. For example, oscillations that occur during tasks (such as the gamma oscillations that occur during a working memory task) are not self-sustaining and therefore would not be included in this construct.

Biological rhythms synchronize to both the internal and external environment. The environment can set/reset these oscillators, and it is important that the internal systems be coordinated with this. Environment includes many things, including food, light, social cues. Social environment is an important cue for humans. For instance, blind people may not be capable of synchronizing with the environment through the light/dark cycle but some have been shown to be able to entrain to social cues. In addition, work with an animal model that is 20 years old has shown that signals normally coming through social interactions can entrain both self and other rhythms.[2]

An important function of circadian clocks is to coordinate across different systems. Repeated cues are needed to synchronize CR, as single cues simply shift the rhythms. The subgroup thought that the interaction of CR between peripheral and central nervous system was important as disruption of central oscillators can lead to mental illness.

Does CR dysregulation lead to mental health problems or do processes that lead to mental health problems also lead to dysregulation of CR? There is evidence to support the link between disruption of CR gene networks and health problems in animals; the research in humans is not as convincing. There is weak evidence from genome-wide association studies that link clock genes with bipolar disorder, depression, etc., but more rigorous studies are required to replicate these findings. In addition, CR dysregulation may be only one manifestation of abnormal clock gene function and may not necessarily mediate the resulting mental health problems.

Matrix elements

When listing the elements that should be included in the Units of Analysis for the CR Construct, the group discussed how to reference clock genes. Over 1000 genes that regulate CR have been identified. For this reason, the group decided to group them into the following four categories:

- Canonical (or Core) Clock Genes
- Clock Associated Genes (associated with clock mechanism but not necessarily fundamental)
- Clock-Controlled Genes (http://bioinf.itmat.upenn.edu/circa)
- Epigenetic Regulation of Clock Genes

Some of these genes may have a relatively minor modulatory effect on the clock and on mental health relevant domains of function. The approach of the RDoC project is to promote translational research relevant to psychopathology, and it is not clear at this stage which genes have an effect on this. Therefore, more work is required to establish the link between CR genes and mental health.

The group identified a list of possible paradigms, of which those most closely related to translational research in mental illness are included in the Circadian Rhythms matrix.

Sleep and Wakefulness

During the discussion of the Sleep and Wakefulness Construct, the group agreed that the definitions and matrix elements needed to be "human-centric," in keeping with the aim of the RDoC project, and focus on mental disorders in humans.

Initially, the group focused on sleep as the main component, but when defining the Construct, it became apparent that the sleep state is primarily defined in relation to the state of wakefulness. The Circadian Rhythms group and the Arousal group agreed that basic biological drives (e.g., eating, drinking) should be included in the "Behavior" Unit of Analysis rather than in the definitions and that different states of wakefulness would be included in the Arousal construct rather than the Sleep and Wakefulness Construct.

The group agreed that sleep was not a unitary state, and its complexity is very important, especially in humans. This complexity includes a group of states that are organized with respect to each other in an invariant order. For example, within sleep there are important transitions (e.g. NREM to REM); there is growing evidence that these transitions are meaningful, point to the highly organized nature of sleep, and are in keeping with cyclic nature of sleep.

The group decided that, despite this growing awareness of the importance of transitions, it was too early to include them in either the definition or the matrix; however, the group thought it was important to mention them in a paragraph in the workshop summary.

Sleep is not simply a "not awake" state. For this reason, the group decided to include in the definition not only its difference from the awake state (perceptual disengagement, unresponsive to environment), but also what is unique to the sleep state. As the discussion proceeded, the group decided that, in reality, we know about the sleep and wake states only in relation to each other. There are brief but distinct transitions when going from sleep to wake and wake to sleep. Abnormalities arise when the two are intermingled with each other and in mixed states. However, there are important transformative effects of sleep on wakefulness and it is important to acknowledge that sleep entails perceptual disengagement. Transformative effects of sleep are distinct from the restorative effects of sleep and include changes to the brain that are not reversible (e.g., the effect of sleep on learning and memory) and which make the brain more effective. Both wake and sleep have separate functions, but the coordination of each with the other is important. However, while it would be difficult, and impractical, for the purposes of this RDoC project, to delineate all the states of wakefulness, it is possible to do this regarding the states of sleep.

There was general agreement that sleep is a response to both homeostatic and circadian systems. Sleep is widespread, but does not necessarily occur at the same time in all brain regions and circuits. For instance, it has been found that some areas of the brain may not be "asleep" as measured by physiology, and there is recent research to suggest that sleep occurs *in vitro* in individual cells.

The group decided that dreaming would not be mentioned in the definition of sleep, but would be included as an element in the self-report column of the matrix, because it is an experiential event during sleep that is relevant to some aspects of mental disorders. For example, one conceptualization of nightmares experienced by individuals with PTSD is that waking experiences cannot be processed during sleep

NIMH encourages comments on any aspect of the workshop and proceedings outlined here. Please send comments to: rdoc@mail.nih.gov

Matrices

Construct name: Arousal

Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-reports
Musarinic receptors (mAChRs, M1-M5) Nicotinic receptors (16 nAChR genes) ACHE CHAT VAChT Serotonin receptors (5HT1-7) 5HTTs Tryptophan Hydroxylase Adrenergic receptors (α1, α2; β1-3) Histamine receptors (H1-4) Dopamine receptors (D1-5) OX1R, OX2R/HCRT1, HCRT2 GABA-A, GABA-B, GABA-C Glutamate Receptors: AMPA, kainate, NMDA, delta; mGluRs Adenosine receptors (A1-3) DBH NET DAT Leptin Ghrelin receptors Cytokine recepors	Glutamate Norepinephrine Acetylcholine Histamine Dopamine Hypocretin/Orexin CRF Serotonin Leptin Ghrelin Opioids Oxytocin Vasopressin Neuropeptide Y GABA Cytokines	Locus Coeruleus Tuberomammillary Nucleus LDT, PPT Basal Forebrain Nuclei Lateral, perifornical, and dorsomedial hypothalamus Dorsal Raphe Ventral Tegmental Area Central Nucleus Amygdala	Cholinergic and monoaminergic Nuclei projections to thalamic and cortical (both neocortical and allocortical/hippocampus circuits). Reciprocoal cholinergic and monoaminergic projection Reciprocal hypothalamic (including hypocretin/orexin, tuberomammillary nucleus) projections to midbrain and pontine monoaminergic and cholinergic nuclei. Hypothalamic to thalamic and cortical circuits Basal forebrain nuclei to cortical circuits Corical circuits such as fronto-insular and dorsal anerior cingulate Brainstem monoaminergic and cholinergic projections to basal forebrain Central Amygdala to monoaminergic and basal forebrain cholinergic nuclei. Reciprocal NTS-Central N. Amygdala Circadian and Sleep-related circuits modulate arousal and are modulated by arousal.	EEG EMG ERPs Autonomic: Heart Rate; Blood Pressure; Pupil Size; Galvanic skin Response; Breathing; etc. HPA Axis: Glucocorticoids; ACTH; CRF. Sex-Specific Differences in Arousal Brain activation as measured by fMRI Neural activity	Waking Startle Eye Blink Motor Activity (increases and decreases) Cognition: learning & memory; attention; executive function; etc. Affective states: anxiety; etc. Agitation Emotional Reactivity Sensory Reactivity Motivated Behavior	Arousal Self-Report Scales (e.g. ADACL, POMS arousal subscale, etc.) Self-assessment Mannequin

Paradigms:

- EEG and EMG recording
- Indices of neural activity such as local field potentials and single neuron recordings
- fMRI/PET
- Psychomotor vigilance and other continuous performance tasks.
- Eye-blink
- Eyelid closure
- Startle
- Odd-ball tasks
- Auditory arousal threshold
- Maintenance of wakefulness test
- Actigraphy and other test of motor activity
- Cortisol awakening response

Construct name: Circadian Rhythms

Genes[A]	Molecules	Cells	Circuits	Physiology	Behavior	Self-Report
Canonical (Core) Clock Genes: Clock; Npas2; Bmal1; Bmal2 Per1,2; Cry1,2; Clock-Associated Genes Rorα, β; Rev-Erbα, β; CK1 δ, ε; CK2 α, β FBXL3 FBXBL21 DEC2, DEC2 Dio2, Dio3 Gsk 3β Per3 Potential additional clock associated genes[1] Clock-controlled genes[1] Receptor genes: NMDAr; AMPAr; 5HTr; GABAr; NPYr; SPr; VPAC1,2; MT1,2; Transcription/ translation factors/ regulators: cFos; JunB; CREB; MAPK; mTOR; PGC1a; miRNA (e.g. miR-206, miR-132) Dbp Epigenetic factors, e.g. Sir2	Input melanopsin; PACAP; Glutamate; GABA; 5HT; NPY; Substance P; Dopamine SCN-synchronizing and modulating agents VIP; AVP; NO; cAMP; cGMP; Calbindin; steroid hormones (estrogen, testosterone, progesterone) Output melatonin; cortisol; AVP; VIP; GABA	ipRGC; rods and cones SCN "clock" cells; Extra-SCN and peripheral tissue cells within the brain (e.g., medium spiny neurons, pars tuberalis cells, fibroblasts) Pineal cells	Input Retinal cells; Retino-hypothalamic tract; Retinogeniculate tract; Raphe to SCN projection; Intrinsic to SCN Suprachiasmatic nucleus (SCN) core/shell Output: SCN projections to: • PVN, DMH, subparaventricular zone, PVT • Central extended amygdala (central nucleus of the amygdala/ Bed nucleus of the stria terminalis) • Hypothalamic neuroendocrine cell groups • Hypothalamic orexin projections[2] • Basolateral amygdala/ Hippo-campus • SCN/PVN/SCG/pineal[2] • HPA axis • Sympathetic/ parasympathe-tic nervous system **Seasonal** • SCN/PVN/SCG/pineal[B]	Gene expression Neural activity Neural transmitters	Locomotor activity Drive-regulated behaviors Sleep-wake Neurobehavioral functions (e.g., alertness, vigilance, affect, learning, memory) Sleep-rated and waking behaviors Masking (e.g., direct effect of environment on activity rhythms)	Phase, diurnal preference, chronotype (e.g., Horne-Ostberg, CTQ) Diary-based measures of daily regularity/ rhythmicity (e.g., Social Rhythm Metric) Sleepiness, alertness, well-being, mood (circadian, seasonal)

[A] Categories of genes relevant to the biological rhythms domain:

1) Canonical (or Core) Clock Genes: Fundamental molecular components of the circadian clockworks based on extensive molecular and genetic studies that constitute cell autonomous transcriptional feedback loops. (Clock-Cry)

2) Clock Associated Genes: Genes for which there is good evidence that they are part of, or can modulate, the fundamental core clock mechanism.

3) Potential additional clock associated genes: Genes that have emerged from genome-wide siRNA screens, e.g., Circadian Screen Database (http://biogps.org/circadian/#goto=welcome)

4) Clock-Controlled Genes: These are genes that are rhythmically driven in abundance by the circadian clock. The subset of clock-controlled genes, typically 10% of the genome varies in a tissue, and perhaps, cell specific pattern. The following databases are available for the following brain regions: suprachiasmatic nuclei,[3] retina.[4] See database for a fuller list of clock-controlled genes in brain regions and other tissues: Circa: Circadian Gene Expression Profiles (http://bioinf.itmat.upenn.edu/circa)

[B] Projection to sleep-relevant structures

Paradigms

- Actigraphy of human circadian rest-activity rhythms in the real world
- Sleep measures (see Sleep-Wake paradigms)
- 24 hour light/dark (LD) cycle (test for entrainment of rhythms)
- T cycles (non-24 hour LD cycles)
- Phase response curve (PRC, phase dependent effects of single light [or other stimulus] pulses delivered at different circadian phases)
- Dim Light Melatonin Onset (DLMO, phase estimate)
- Acute melatonin suppression by light (relative index of the sensitivity of the circadian system to light, e.g. wavelength, intensity, duration curves)
- Pupillary light reflex (acute measure of rod, cone and melanopsin photosensitivity).
- Sensory threshold testing (ERG, ERP, etc.)
- Bioluminscent/fluorescent real-time gene expression imaging
- Masking (e.g., sleep effect on cognitive behavioral therapy)
- Genetic Approaches – genome-wide association study, candidate gene, epigenomics, circadian genomics (temporal gene expression), mutagenesis, gene targeting, quantitative trait loci.

Construct name: Sleep-Wakefulness

Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-Report
• Circadian Rhythms genes (see Circadian Rhythms table) • Genes relevant to arousal (see Arousal table) • Genes with sleep-specific effects: Per3, Clock, Sur2, Dec2	Neurotransmitters and neuromodulators, including • Acetylcholine • Norepinephrine • Serotonin • Dopamine • Histamine • GABA • Galanin • Adenosine • Hypocretin/Orexin • Glutamate • CRF • Vasopressin • NPY • Cytokines	• Lateral and perifornical hypothalamus • Anterior hypothalamus and basal forebrain • Posterior hypothalamus (TMN) • Brainstem (e.g., LC, Raphe, LDT/PPT, , VTA) • Thalamus (median thalamic nuclei, reticular nucleus)	**Wakefulness** • Arousal circuits also subserve wakefulness (see Arousal table) • Circadian Rhythms circuits also subserve the organization of sleep and wakefulness (See Circadian Rhythms table) **Sleep** NREM sleep (forebrain) • Basal forebrain and anterior hypothalamus projections to arousal promoting cell groups • Thalamo-cortical circuits REM sleep (brainstem) • Mesopontine nuclei, especially regions ventral to locus coeruleus	• Brain electrical activity (EEG) (spindles, slow waves, theta) • Brain metabolic activity • Electromyographic activity (EMG) • Electro-oculography (EOG) • Things modulated by/ that happen during sleep (hormones [e.g., GH, prolactin, gonadotropins, etc.], other aspects of systemic physiology) • NREM and REM sleep, wakefulness, and their transitions • Temporal and topographic organization of sleep dynamics • Temporal and topographic organization of homeostatic sleep drive during sleep • Physiological sleep propensity (sleep latency) • Capacity for wakefulness under low stimulation) • Physiologic measures of sleepiness, homeostatic sleep drive during waking • Sex-specific sleep physiology	• Sleep (duration, continuity/ fragmentation, architecture), wakefulness • Sleep deprivation and satiation • Sleep timing and variability • Rest-activity patterns (actigraphy) • Sleep inertia • Sleep-dependent neurobehavioral functions (e.g., memory consolidation, affect, affect regulation, alertness, vigilance, impulsivity, risk-taking) • Motor behaviors during sleep • Intermediate/ admixed sleep-wake states • Sensory arousal threshold • Co-sleeping • Sex-specific sleep behaviors	• Sleep quality, restoration, quantity (e.g., insomnia, hypersomnia) • Sleep timing • Alertness, sleepiness • Fatigue • Dream reports • Specific sleep symptoms • Sleep-modulated symptoms (e.g., mood, alertness)

Paradigms:

- EEG (e.g., sleep staging, quantitative EEG, topographic mapping, source localization)
- MEG
- TMS
- Nocturnal polysomnography (may include measures of respiration, heart rate variability, other)
- Arousal threshold testing
- Multiple sleep latency testing
- Maintenance of wakefulness testing
- Measurement of slow eye movements during wakefulness (physiologic measures of sleepiness, homeostatic sleep drive)
- Locomotor activity (e.g., actigraphy)

- Total, partial, and stage-selective deprivation paradigms
- Non-24-hour sleep-wake schedules (e.g., forced desynchrony, ultrashort schedules)
- Neurobehavioral testing in relation to sleep
- Sleep-dependent memory consolidation, fear extinction
- Functional imaging techniques: e.g., fMRI, PET, MEG, high-density EEG
- Self-report methods include retrospective symptom and sleep reports, daily sleep diaries

Default Mode Network

As noted above, the NIMH RDoC working group decided that this construct was not appropriate for inclusion because of the lack of specificity of the identified circuits among intrinsic neural networks and their ambiguous link to behavior and psychopathology. The summary of the workshop group's deliberations is included here to serve as a starting point for future possible consideration as a Construct.

Definition: The Default Mode Network (DMN) can be conceptualized as an organized, spontaneous network of neural activity that is modulated during attention-demanding cognition.

The Default Mode Network (DMN) is a set of brain regions which

a. are characterized by temporally correlated, low-frequency, spontaneous BOLD signal fluctuations which tend to inversely correlate with fluctuations in other networks, including those that subserve arousal, attention, perception, and working memory;
b. show consistent suppression of activity during most cognitive tasks but increase in activation during certain tasks, including episodic memory retrieval, introspection, and self-referential processing;
c. vary in degree of activation and connectivity related to individual differences in cognition and behavior, including psychopathology and neurological impairment; and,
d. are one of many Intrinsic Connectivity Networks (ICNs) that can be identified in resting-state fMRI and PET analyses.

Default Readiness

The group focused its initial discussions on identifying a Construct that is related to self-referential, non-task focused processes and which is defined broadly enough to be informative but not so broadly that it encompasses the whole brain and pervasive, synchronous neurophysiological oscillations.

Is it a Construct?

The group began by discussing the construct that was drafted by the RDoC working group (Default Readiness) and there was consensus that it was too vague; the concept of "readiness" was unclear in its relationship to arousal; and, the use of the term "default" conjured the Default Mode Network (DMN) but did not specify it. The concept of brain readiness is orthogonal to many of the existing RDoC Constructs and could be thought of as the regulation of various networks, rather than a circuit/construct in and of itself. The group discussed whether they should focus on defining a construct or whether they should instead define a cross-cutting element (i.e., a new method/tool that could be represented in a column in the RDoC matrix) which would be relevant to other constructs but would not be an independent construct. It was noted that this construct was distinct from other RDoC constructs because it is a relatively new area of investigation, and it is the only one that is based primarily on findings from neuroimaging

studies. Ultimately, the group moved forward to define a construct that reflects some fundamental organizational principles of the brain that is related to but sufficiently distinct from other constructs with the goal of "setting the stage" for ongoing research in the area.

Is it a circuit?

The DMN is a neural circuit that can be identified in individuals who are not engaged in a task, but it is not the only such network. Although the findings regarding specific nodes of the DMN have been robust, there are conflicting reports in the literature regarding whether the DMN is indeed a single network.[5, 6] It is possible, for example, to identify areas of co-occurring, oscillating activity in various neural networks by seeding regions whose activity is recorded during between-task rest periods. These networks depend, to some extent, on the nature of the task being performed, and thus activation during periods of rest lacks some specificity. The DMN could be identified as a prototypical network related to readiness to mount a response, but interactions with non-DMN brain regions have not yet been thoroughly elaborated. The group considered identifying the DMN as an exemplar/prototype of a more general construct such as Intrinsic Connectivity Networks (ICN) and the many processes that govern the ways in which various networks are integrated and modulated, taking into consideration the emerging literature which suggests that there are other networks that could be considered to be ICN. It was ultimately decided that whole-brain dynamics is not suitable as a construct (there would be no specific circuits or neurotransmitters and many genes involved) but, instead, the DMN would be defined as the construct, reflecting the dynamic regulation of networks which can reasonably be considered to be conceptually independent from other constructs, by representing an important basic brain function that is strongly related to psychopathology and that including it as a separate construct will help to focus future research in this field.

The DMN Construct was thought to be sufficiently narrow and to reflect the unique aspects of DMN as it is related to moment-to-moment differences in task- versus non-task focus, related to variations in task performance, and related to other, task-related networks. This Construct is related to the Arousal/Regulatory domain because it concerns the ongoing allocation of resources. Generally, activity in the DMN decreases with task difficulty, possibly because it is more challenging to sustain interoceptive activities during more difficult tasks. There is some evidence that the activity of the DMN is distinct from arousal-related activity. The relationship between DMN activity and arousal mechanisms is, however, an area of active research. Future work will clarify whether there is a linear relationship between DMN activity and arousal or the relationship is modulated differently by high compared to medium degrees of arousal.

The definition of DMN includes a description of the DMN as one of many ICNs. ICNs are "organized," including spatial and temporal organization, and are intended to include both local and distributed networks. It was noted that the networks are interactive in nature, and affected by ongoing neuroplasticity and changes within the networks. In the definition of DMN and the description of ICNs, "cognition" and "behavior" were considered by the group to be broadly defined and inclusive.

Attention, resting state, and interoception

The group discussed existing uncertainties about the specific function(s) the DMN serves, and various ambiguities in the understanding of terminology used in this research area. It can be difficult to disambiguate the function of the DMN and attention (which is a Construct in the Cognitive Systems domain). The tasks that are often used to study non-task DMN usually involve some degree of arousal and attention, but the relationships between arousal, attention, and DMN have not generally been studied explicitly. Considering a clinical example, a patient who can't manage to complete their daily activities because they are preoccupied by internal thoughts (or a patient who is preoccupied by paranoid thoughts) could be characterized as experiencing either malfunction of the DMN or attentional impairment. The relationship between attention and DMN is somewhat uncertain, but there is some evidence that the DMN is distinct from networks that subserve attention. Rather than being related to higher-level cognition (such as planning), DMN may be more closely linked to more basic biological rhythms and consciousness, especially in light of observed changes in anti-correlations in the DMN during anesthesia. The DMN's infra-slow fluctuations might be physiologically significant, perhaps related to more basic cellular or synaptic functions (e.g., to maintain activity and avoid pruning).

It was noted that individuals alternate the allocation of their attention between internally and externally generated stimuli on an ongoing basis, but the DMN Construct was not intended to refer selectively to an interoceptive focus. For example, it is possible to be focused on internal stimuli, such as autonomic activity and cognitive reactions to such activity, which would suppress DMN activity or, conversely, to appear focused on an external stimulus while simultaneously being engaged in mind wandering or stimulus-free thinking which would be consistent with DMN activation. One way of thinking about DMN is to consider that DMN activation may occur when the brain simply isn't doing something else, whether that "anything else" is internal or externally directed.

Another important distinction was made between DMN and "resting state." Although these terms are sometimes used synonymously, they are not overlapping and there was good agreement in the group that "resting state" is a method/paradigm that can be used for interrogating the degree of integrity of various networks that are relevant for a variety of constructs, but it not a network or a construct in and of itself. DMN is one of many networks that can be identified using resting state methodology, but the activation of the network is apparent in research paradigms other than resting state.

The group discussed the psychological features that would characterize this construct and, drawing from Peter Fransson's 2005 paper, focused on the ability to "turn off" or disengage the DMN in order to toggle attention between introspection and externally focused readiness.[7] It was considered whether the unique feature of the DMN construct is the distinction between rest and non-rest. It is difficult, however, to define the boundaries between rest and non-rest, because participants may be engaged in a variety of covert activities during periods of task engagement or non-engagement which could engage different neural systems.[8] Different studies have addressed this issue using various methodologies, such as instructing participants to engage in internally-focused tasks (e.g., pondering their future, retrieval of personal memories) or

daydreaming, although the role of spontaneity, in contrast to directed tasks, in generating DMN activity is not yet known. DMN could be thought of as an individual's "set point" in the absence of goal-directed behavior such that DMN predominates when no goal is present but is suppressed when a goal is present. Although "rest" is heterogeneous and individuals will vary from one another and over time in their mental activities during rest, consistent patterns of activation have been detected, suggesting it is a robust network. During the discussion, the Construct and its definition evolved away from focusing on the "switching" or "on-off" aspects of the DMN as being potentially misleading, because the intention was to focus on the state of DMN activation that precedes or follows "switching," incorporating the switching as a property of but not the entirety of the Construct.

The group considered other possible constructs, including "mind-wandering" and "task-independent mentation," but it was felt that these did not fully capture the Construct, and there is evidence that some tasks increase DMN and some decrease it.

Task performance, individual differences and psychopathology

Because one of the goals of the RDoC initiative is to improve the classification of participants in research on mental disorders, the group discussed the extent to which studies have identified individual differences in various features of DMN activity and modulation.[9, 10] The speed and degree to which DMN activity is modulated could reflect individual differences in how competition between tasks is managed. Also, the degree of anti-correlation between activity in the DMN and activity in other networks is related to task performance and changes over the lifespan. The DMN is identifiable early in childhood, and it changes during development and with aging.

Rather than focusing on relationships between specific tasks and DMN activity, the recent literature suggests a more general property of the DMN, specifically, that the activation of the DMN comes as a cost to engagement in and meeting the demands of other tasks, and so there are many ways to interrogate the DMN. The rate, phase and amplitude of oscillations within the DMN may play a role in modulating cognition and behavior. These DMN characteristics have been found to be related to visual perception as well as various aspects of task performance, including the force of responding.[11] The ability to suppress DMN activity is associated with working memory and performance on other types of tasks, links which could be relevant to certain types of psychopathology.

Disruptions in DMN activity have been detected in many different disorders/conditions but the closest links to pathology are in neurological rather than psychiatric patients. Some of the most robust clinical findings involve abnormalities observed in Alzheimer's disease, including alterations in DMN activity and reduced connectivity among nodes in the DMN, but DMN abnormalities in Alzheimer's disease appear to be related to disease stage. Alterations in DMN activity have also been reported in individuals with insomnia and with concussion.[12]

With regard to mental disorders, DMN activity has not been studied extensively in un-medicated patients, but task-related suppression of DMN has been found to be reduced in relatives of

individuals with schizophrenia.[13] Although there is some evidence that activity in the DMN (and temporal lobe) can be used to help differentiate bipolar disorder from schizophrenia[14], there is also evidence that abnormalities in DMN activity are related to various aspects of psychopathology that may not map onto traditional diagnostic categories, which would be consistent with its inclusion in RDoC.

Interpretation of the BOLD signal

Because the empirical basis for this construct rest primarily upon findings from neuroimaging studies, the challenges of interpreting the blood oxygenation-level dependent (BOLD) signal with regard to neural activity were discussed. Although novel techniques have provided empirical support for the relationship between the BOLD signal and cellular activity[15, 16], it was noted that deactivation and suppression are somewhat difficult terms to define when considering the comparative/subtractive nature of functional magnetic resonance imaging (fMRI) analyses.[17] The areas of activation observed during studies of the DMN may be due to a combination of increased activity as well as suppression of activity, and these types of interactions complicate the interpretation of measures of the magnitude of activity as well as the results of correlational analyses. Similarly, further studies are needed to differentiate between areas of hyperconnectivity and areas of hyperactivity. There remains some ambiguity in interpreting differences in activation observed during different tasks in purportedly "task-negative" networks.[18]

Matrix elements:

Genes: Heritability of the functioning connectivity of the DMN has been demonstrated[19], however, the specific genes involved in the connectivity have not been identified. There are an increasing number of reports of studies that report genetic associations with the DMN, but few of those studies are systematic or replicated as of yet, so the group was conservative in listing genes that have been preliminarily identified as being related to DMN.

Circuit: Although there is some relationship between structural and functional connectivity among regions involved in DMN, there are some interesting exceptions and the functional and structural networks do not always overlap completely. Some nodes are closely connected and others are not. Because DMN activity is so widely distributed, it is difficult to identify a single network that is associated with DMN. Functional connectivity may reflect direct/single synapse or indirect/multiple synapse links. Although the nodes are not spatially contiguous, they appear to be functionally linked.[20] Future studies will help understand why this network is so much more distributed than other networks (e.g., sensory) and the functions that these connections between distributed structures serve.

Anti-correlated networks could also be considered to be part of this circuit, although the relationship between anti-correlated networks and DMN awaits further study. Since anti-correlated networks are task-positive during some tasks, it is not clear whether they should be considered part of the circuit.

Physiology: Although much of the research on the DMN has been conducted using fMRI, it can also be studied using electrophysiological methods (linking slow electroencephalography (EEG) fluctuations with differences in performance) and/or multimodal imaging [21, 22]. It was noted that infra-slow oscillations of 0.1 Hz and below, which are difficult to measure using EEG could be related to fluctuations in gamma and have been studied in rodents and non-human primates. Some research groups have studied infra-slow oscillations in humans using scalp direct current (DC; <0 .1 Hz) EEG recordings, combined EEG and fMRI, simultaneous transcranial magnetic stimulation (TMS) and fMRI, transcranial direct current stimulation (tDCS), electrocorticography (eCOG), or optical imaging. The group felt it was important to be inclusive of modalities for studying the physiology of this construct.

Self-reports: Although there is an exhaustive list of different self-report measures that might be relevant to DMN studies, only a few of the more established ones are included in the matrix.

Paradigms: Many paradigms can be used to study DMN, and many of those are already included in other Constructs (e.g., working memory). Therefore, the group focused on those that are more specifically focused on this construct (e.g., autobiographical memory, self-referential thought) It was noted that the order of tasks can impact results due to carry-over and sustained changes in brain activity and contamination of resting activity by preceding task(s).[23]

Areas for further investigation

During their discussions, the group identified several areas that are in need of further investigation with regard to the DMN:

- What is the significance of the low frequency of DMN activation? Is there a physiological importance of this frequency to, for example, the persistence versus elimination of synapses in the context of ongoing neuroplasticity [24]?

- Does the inverse correlation between DMN and identified regions carry over to regions such as the amygdala and basal ganglia? More broadly, what is the relationship between DMN and motivation/affect, and the relationship to control networks [25]?

- What is the relationship between exteroceptive versus interoceptive focus and spontaneous versus directed or task-related activity and DMN activation?

- What engenders the transition between DMN activation state(s) and non-DMN state(s), and to what extent is the ability to make that transition important to psychopathology?

- To what extent does DMN activity relate to and/or interact with arousal mechanisms and biological rhythms (e.g., does DMN increase under conditions of high arousal)?

- What are the genetic, molecular, and cellular substrates of the DMN?

- To what extent is the DMN affected/changed by experience-dependent/learning-related changes?

Construct name: Default Mode Network

Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-reports
Apoe4 carriers have altered DMN [26]	Amyloid plaque deposition overlaps with DMN [27, 28] GABA levels associated with negative BOLD signal change in medial prefrontal [29]	Some relationships observed between anatomical connectivity and resting state connectivity in the DMN e.g., [30], but with some exceptions.	The DMN includes the following, widely distributed anatomic regions: Medial Prefrontal Posterior Cingulate Precuneus Medial Temporal Inferior Lateral Parietal [31-34]	Relationship of electrical activity to BOLD fluctuations [16] Highly metabolically active [33] Inversely connected/coupled to other networks [7, 34, 35] Phase and/or amplitude of oscillations of spontaneous activity may modulate cognition and behavior [9] Macaque posterior cingulate firing reduces during task [24] Low-frequency gamma power	Episodic memory retrieval [5] Self referential processing [41] Degree of suppression is related to task difficulty and better task performance – Example of individual difference [10, 42-44] Strength of anti correlation with task positive network predicts better task performance [45] Lack of task suppression of DMN in psychopathology [13, 46] Reduced DMN connectivity in	Mind wandering during scan correlated with the DMN [48] Stimulus independent thought[49] Rumination and depression [50-52]

				fluctuations are correlated across electrodes [36] Scalp EEG shows alpha and beta power fluctuations correlated with resting state networks [37] Infra-slow oscillations – scalp DC EEG (< 0.1 Hz) [38, 39] MEG correlation with beta frequency [21, 22] While stable over subjects, the correlations are not stationary [40]	Alzheimer's disease [27, 47]	

Paradigms:

- Lie in scanner without task or stimulus;
- Autobiographical memory
- Self-referential thought
- Eyes open > eyes closed comparison
- Application of TMS to alter network functioning
- tDCS
- Pharmacological challenges
- Simultaneous EEG/fMRI recording
- MEG
- eCog
- Optical imaging (animal)
- Real-time fMRI feedback to modulate network

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References

1. Sanford LD, Tang X, Xiao J, Ross RJ, Morrison AR. GABAergic Regulation of REM Sleep in Reticularis Pontis Oralis and Caudalis in Rats. J Neurophysiol. 2003; 90(2):938-45.
2. Goel N, Lee TM. Relationship of circadian activity and social behaviors to reentrainment rates in diurnal Octodon degus (Rodentia). Physiol Behav. 1996; 59(4–5):817-26.
3. Panda S, Antoch MP, Miller BH, Su AI, Schook AB, Straume M, et al. Coordinated Transcription of Key Pathways in the Mouse by the Circadian Clock. Cell. 2002; 109(3):307-20.
4. Storch K-F, Paz C, Signorovitch J, Raviola E, Pawlyk B, Li T, et al. Intrinsic Circadian Clock of the Mammalian Retina: Importance for Retinal Processing of Visual Information. Cell. 2007; 130(4):730-41.
5. Kahn I, Andrews-Hanna JR, Vincent JL, Snyder AZ, Buckner RL. Distinct Cortical Anatomy Linked to Subregions of the Medial Temporal Lobe Revealed by Intrinsic Functional Connectivity. J Neurophysiol. 2008; 100(1):129-39.
6. Meda SA, Gill A, Stevens MC, Lorenzoni RP, Glahn DC, Calhoun VD, et al. Differences in resting-state functional magnetic resonance imaging functional network connectivity between schizophrenia and psychotic bipolar probands and their unaffected first-degree relatives. Biol Psychiatry. 2012; 71(10):881-9.
7. Fransson P. Spontaneous low-frequency BOLD signal fluctuations: An fMRI investigation of the resting-state default mode of brain function hypothesis. Hum Brain Mapp. 2005; 26(1):15-29.
8. Smith SM, Fox PT, Miller KL, Glahn DC, Fox PM, Mackay CE, et al. Correspondence of the brain's functional architecture during activation and rest. Proc Natl Acad Sci U S A. 2009; 106(31):13040-5.
9. Boly M, Balteau E, Schnakers C, Degueldre C, Moonen G, Luxen A, et al. Baseline brain activity fluctuations predict somatosensory perception in humans. Proc Natl Acad Sci U S A. 2007; 104(29):12187-92.
10. McKiernan KA, Kaufman JN, Kucera-Thompson J, Binder JR. A Parametric Manipulation of Factors Affecting Task-induced Deactivation in Functional Neuroimaging. J Cog Neurosci. 2003; 15(3):394-408.
11. Fox MD, Snyder AZ, Vincent JL, Raichle ME. Intrinsic Fluctuations within Cortical Systems Account for Intertrial Variability in Human Behavior. Neuron. 2007; 56(1):171-84.
12. Buysse DJ, Germain A, Hall M, Monk TH, Nofzinger EA. A Neurobiological Model of Insomnia. Drug Discovery Today: Disease Models. 2011; 8(4):129-37.
13. Whitfield-Gabrieli S, Thermenos HW, Milanovic S, Tsuang MT, Faraone SV, McCarley RW, et al. Hyperactivity and hyperconnectivity of the default network in schizophrenia and in first-degree relatives of persons with schizophrenia. Proc Natl Acad Sci U S A. 2009; 106(4):1279-84.
14. Calhoun VD, Maciejewski PK, Pearlson GD, Kiehl KA. Temporal lobe and “default” hemodynamic brain modes discriminate between schizophrenia and bipolar disorder. Hum Brain Mapp. 2008; 29(11):1265-75.
15. Lee JH, Durand R, Gradinaru V, Zhang F, Goshen I, Kim D-S, et al. Global and local fMRI signals driven by neurons defined optogenetically by type and wiring. Nature. 2010; 465(7299):788-92.

16. Shmuel A, Leopold DA. Neuronal correlates of spontaneous fluctuations in fMRI signals in monkey visual cortex: Implications for functional connectivity at rest. Hum Brain Mapp. 2008; 29(7):751-61.
17. Hayes DJ, Huxtable AG. Interpreting deactivations in neuroimaging. Front Psych. 2012; 3.
18. Spreng RN. The fallacy of a “task-negative” network. Front Psych. 2012; 3:Article 145.
19. Glahn DC, Winkler AM, Kochunov P, Almasy L, Duggirala R, Carless MA, et al. Genetic control over the resting brain. Proc Natl Acad Sci U S A. 2010; 107(3):1223-8.
20. Honey CJ, Sporns O, Cammoun L, Gigandet X, Thiran JP, Meuli R, et al. Predicting human resting-state functional connectivity from structural connectivity. Proc Natl Acad Sci U S A. 2009; 106(6):2035-40.
21. de Pasquale F, Della Penna S, Snyder Abraham Z, Marzetti L, Pizzella V, Romani Gian L, et al. A Cortical Core for Dynamic Integration of Functional Networks in the Resting Human Brain. Neuron. 2012; 74(4):753-64.
22. Hipp J, Hawellek D, Corbetta M, Siegel M, Engel A. Large-scale cortical correlation structure of spontaneous oscillatory activity. Nat Neurosci. 2012; 15(6):884-90.
23. Visscher KM, Miezin FM, Kelly JE, Buckner RL, Donaldson DI, McAvoy MP, et al. Mixed blocked/event-related designs separate transient and sustained activity in fMRI. NeuroImage. 2003; 19(4):1694-708.
24. Fellin T, Halassa MM, Terunuma M, Succol F, Takano H, Frank M, et al. Endogenous nonneuronal modulators of synaptic transmission control cortical slow oscillations in vivo. Proc Natl Acad Sci U S A. 2009; 106(35):15037-42.
25. Harrison BJ, Pujol J, Ortiz H, Fornito A, Pantelis C, Yücel M. Modulation of Brain Resting-State Networks by Sad Mood Induction. PLoS ONE. 2008; 3(3):e1794.
26. Sheline YI, Morris JC, Snyder AZ, Price JL, Yan Z, D'Angelo G, et al. APOE4 Allele Disrupts Resting State fMRI Connectivity in the Absence of Amyloid Plaques or Decreased CSF Aβ42. J Neuro. 2010; 30(50):17035-40.
27. Buckner RL, Snyder AZ, Shannon BJ, LaRossa G, Sachs R, Fotenos AF, et al. Molecular, Structural, and Functional Characterization of Alzheimer's Disease: Evidence for a Relationship between Default Activity, Amyloid, and Memory. J Neuro. 2005; 25(34):7709-17.
28. Vlassenko AG, Vaishnavi SN, Couture L, Sacco D, Shannon BJ, Mach RH, et al. Spatial correlation between brain aerobic glycolysis and amyloid-β (Aβ) deposition. Proc Natl Acad Sci U S A. 2010; 107(41):17763-7.
29. Northoff G, Walter M, Schulte RF, Beck J, Dydak U, Henning A, et al. GABA concentrations in the human anterior cingulate cortex predict negative BOLD responses in fMRI. Nat Neurosci. 2007; 10(12):1515-7.
30. Hagmann P, Cammoun L, Gigandet X, Meuli R, Honey CJ, Wedeen VJ, et al. Mapping the Structural Core of Human Cerebral Cortex. PLoS Biol. 2008; 6(7):e159.
31. Shulman GL, Astafiev SV, McAvoy MP, d'Avossa G, Corbetta M. Right TPJ Deactivation during Visual Search: Functional Significance and Support for a Filter Hypothesis. Cereb Cortex. 2007; 17(11):2625-33.
32. Gusnard DA, Raichle ME. Searching for a baseline: Functional imaging and the resting human brain. Nat Rev Neurosci. 2001; 2(10):685-94.
33. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. Proc Natl Acad Sci U S A. 2001; 98(2):676-82.

34. Greicius MD, Krasnow B, Reiss AL, Menon V. Functional connectivity in the resting brain: A network analysis of the default mode hypothesis. Proc Natl Acad Sci U S A. 2003; 100(1):253-8.
35. Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc Natl Acad Sci U S A. 2005; 102(27):9673-8.
36. Leopold DA, Murayama Y, Logothetis NK. Very Slow Activity Fluctuations in Monkey Visual Cortex: Implications for Functional Brain Imaging. Cereb Cortex. 2003; 13(4):422-33.
37. Laufs H, Krakow K, Sterzer P, Eger E, Beyerle A, Salek-Haddadi A, et al. Electroencephalographic signatures of attentional and cognitive default modes in spontaneous brain activity fluctuations at rest. Proc Natl Acad Sci U S A. 2003; 100(19):11053-8.
38. Helps SK, Broyd SJ, James CJ, Karl A, Chen W, Sonuga-Barke EJS. Altered spontaneous low frequency brain activity in Attention Deficit/Hyperactivity Disorder. Brain Res. 2010; 1322(0):134-43.
39. Monto S, Palva S, Voipio J, Palva JM. Very Slow EEG Fluctuations Predict the Dynamics of Stimulus Detection and Oscillation Amplitudes in Humans. J Neuro. 2008; 28(33):8268-72.
40. Chang C, Glover GH. Time–frequency dynamics of resting-state brain connectivity measured with fMRI. NeuroImage. 2010; 50(1):81-98.
41. Gusnard DA, Akbudak E, Shulman GL, Raichle ME. Medial prefrontal cortex and self-referential mental activity: Relation to a default mode of brain function. Proc Natl Acad Sci U S A. 2001; 98(7):4259-64.
42. Singh KD, Fawcett IP. Transient and linearly graded deactivation of the human default-mode network by a visual detection task. NeuroImage. 2008; 41(1):100-12.
43. Anticevic A, Repovs G, Shulman GL, Barch DM. When less is more: TPJ and default network deactivation during encoding predicts working memory performance. NeuroImage. 2010; 49(3):2638-48.
44. Polli FE, Barton JJS, Cain MS, Thakkar KN, Rauch SL, Manoach DS. Rostral and dorsal anterior cingulate cortex make dissociable contributions during antisaccade error commission. Proc Natl Acad Sci U S A. 2005; 102(43):15700-5.
45. Hampson M, Driesen N, Roth JK, Gore JC, Constable RT. Functional connectivity between task-positive and task-negative brain areas and its relation to working memory performance. MRI. 2010; 28(8):1051-7.
46. Kennedy DP, Redcay E, Courchesne E. Failing to deactivate: Resting functional abnormalities in autism. Proc Natl Acad Sci U S A. 2006; 103(21):8275-80.
47. Greicius MD, Srivastava G, Reiss AL, Menon V. Default-mode network activity distinguishes Alzheimer's disease from healthy aging: Evidence from functional MRI. Proc Natl Acad Sci U S A. 2004; 101(13):4637-42.
48. Mason MF, Norton MI, Van Horn JD, Wegner DM, Grafton ST, Macrae CN. Wandering Minds: The Default Network and Stimulus-Independent Thought. Science. 2007; 315(5810):393-5.
49. McGuire P, Paulesu E, Frackowiak R, Frith C. Brain activity during stimulus independent thought. Neuroreport. 1996; 7(13):2095-9.
50. Sheline YI, Price JL, Yan Z, Mintun MA. Resting-state functional MRI in depression unmasks increased connectivity between networks via the dorsal nexus. Proc Natl Acad Sci U S A. 2010; 107(24):11020-5.

51. Greicius MD, Flores BH, Menon V, Glover GH, Solvason HB, Kenna H, et al. Resting-State Functional Connectivity in Major Depression: Abnormally Increased Contributions from Subgenual Cingulate Cortex and Thalamus. Biol Psychiatry. 2007; 62(5):429-37.
52. Hamilton JP, Furman DJ, Chang C, Thomason ME, Dennis E, Gotlib IH. Default-Mode and Task-Positive Network Activity in Major Depressive Disorder: Implications for Adaptive and Maladaptive Rumination. Biol Psychiatry. 2011; 70(4):327-33.