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EDITORIAL

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New horizons in emotional well-being and brain aging: Potential lessons from cross-species research

Key points

- Emotional wellbeing (EWB) is a multi-faceted concept of immediate relevance to human health.
- NEW Brain Aging Center focuses on mechanistic understanding of EWB in relation to brain aging.
- A reactivity and reappraisal model can serve the understanding of EWB and its age-related changes.

1 | REEXAMINING EWB IN RELATION TO BRAIN AGING

In early 2021, the NIH funded six research networks to advance emotional wellbeing (EWB) research, topics of which range from mechanistic, clinical, to population research in families, health care-related financial burden, or brain aging. EWB is defined by the network of networks as "a multi-dimensional composite that encompasses how positive an individual feels generally and about life overall. It has both experiential features such as the emotional quality of momentary and everyday experiences and reflective features such as judgments about life satisfaction, sense of meaning, and ability to pursue goals that can include and extend beyond the self. These features occur in the context of culture, life circumstances, resources, and life course."[1]

EWB research in the context of brain aging raises fascinating new questions. It is well known that selective physiological degeneration occurs in the typical aging process,[2] with advanced brain aging[3] or extra pathologies[4] leading to neurodegenerative diseases. At the system level, various imaging techniques have been employed to quantify these typical and pathological structural and functional changes of the brain and to link these to behavioral consequences. Example changes include selective grey and white matter loss,[5] whole brain atrophy,[6] brain functional dedifferentiation,[7] posterior-to-anterior brain hub shifting[8] in typical aging, as well as dementia pathologies[9] in various pathological aging. It seems a paradox[10] that, different from most cognitive capacities, EWB in the typical old agers (TOAs) is not affected by the advanced brain aging; instead, typical aging process is often accompanied by increases in overall EWB.[11,12] Understanding how TOAs process emotion to maintain, or even improve multi-dimensional composites of EWB, especially emotional processes that are resistant to or resilient from the effects of brain aging, can be particularly informative for novel therapeutic development addressing behavioral disturbances in groups with pathological aging or mental disorders in general.

There have been various theories concerning domain (focusing on elaborating domains of content involved in EWB), function (focusing on behavioral or neural functions underpinning or regulating EWB), construct (focusing on operational attributes composing the construct of emotion), or psychophysiology (focusing on psychophysiology mechanisms influencing emotion) of emotional processes that provide implications related to aging (Table 1). The replication and reproducibility in aging and EWB research are overall limited since most of the theories were not developed for understanding brain aging or directly concerning EWB. This paper therefore presents an approach to study issues involved in EWB and brain aging research through cross-species behavior-brain-psychophysiology research.

2 | ACTIONS AND BRAIN CIRCUITS OF EMOTIONAL PROCESSING IN RELATION TO EWB IN TYPICAL OLDER ADULTS

We selectively reviewed human literature, comparing TOAs with younger adults, or with older adults with mental disorders, to elaborate emotional processing's role in EWB among TOAs. We consider behavioral and psychophysiological reactivity equally important for initial responses to emotional stimuli. Comparing TOAs versus younger adults as well as TOAs versus older adults with pathological changes, the literature seems consistent that TOAs have reduced affective arousal overall,[25] increased positive valence,[25,26] and avoidance of negative emotional stimuli both behaviorally and psychophysiologically.[27,28] In parallel, limited brain imaging studies, primarily task-related or resting-state fMRI, examined brain correlates of the reactivity in TOAs. TOAs have increased regional activation or network strength of ventral attention network (VAN) (a.k.a., Salience network), default mode network (DMN), and amygdala to positive stimuli, and decreased regional activation (e.g., amygdala and hippocampus) or network strength (e.g., DMN) to negative stimuli.[25–27,29–32] Of note, emotional stimuli can come from physiological and psychosocial domains. A recent meta-analysis of neural correlates of physiological and psychosocial stress reactivity across adulthood revealed that inferior frontal gyrus (part of ventromedial prefrontal cortex/vmPFC, a region

TABLE 1 Implications of emotional processes related theories for aging and EWB.

Domain-driven approach	• Life satisfaction[13] • Sense of purpose[14] • Positive affect[15] • Locus of control[16]
Function-oriented approach	• Appraisal theories[17] • Emotion regulation network[18] • Plasticity of well-being[19] • Aging-related strength versus vulnerability[20]
Construct-based approach	• Short-term affective dynamics (i.e., variability, instability, inertia, and reactivity)[21] • Emotion primitives (valence, persistence, intensity, and generalization)[22]
Psychophysiology-implied approach	• Interoception[23] • Allostatic load stress model[24]

of DMN and VAN) and anterior insula (a region of VAN) are activated across both stressor types, while striatum is functionally specific with dorsal striatum activated during physiological stress and ventral striatum deactivated during psychosocial stress.[33]

Further, understanding reappraisal, processes of elaborating, controlling, and/or adapting to reactivity, may inform the relationship between reactivity and experienced EWB in a single event, as well as between reactivity and evaluative EWB throughout repeated events in old age. Charles's Strength and Vulnerability Integration model suggests two separate pathways—changes in life perspective and reduced physiological flexibility—occur in the aging process.[20] Within a single stressful event, reduced physiological flexibility will not immediately dominate the emotional regulation process if the life perspective, or reappraisal engages effectively. This process may explain the linkage between reactivity and experienced EWB. Second, McEwen's allostatic load model elaborates an adaptation related chronic process.[34] That is, during repeated stressful events, regardless of the degree of reactivity, a positive adaptation via utilizing effective reappraisal may help explain the maintenance of experienced EWB. Emerging studies support pieces of actions, including memory encoding and retrieval of positive stimuli,[35,36] semantic evaluation of positive and negative stimuli,[37,38] and cognitive control or inhibition for negative stimuli[27,39,40] involved in reappraisal in TOAs. Of note, these cortical brain regions involved in actions of reappraisal are primarily from or shared by regions (e.g., anterior cingulate cortex, subregions of prefrontal cortex) or networks of DMN and frontoparietal control network (FPCN).[27,35–40]

Together, ventromedial prefrontal cortex (vmPFC) seems to engage multiple networks (FPCN, DMN, VAN, and subcortical regions) to regulate reactivity and reappraisal to emotional stimuli and relate to EWB in TOAs. Regardless, a major gap in the brain and EWB literature is the difficulty in establishing a mechanistic relationship between EWB and typical and pathological aging brains. Uchino et al summarize two perspectives potentially behind the changes in reactions to emotional stimuli in old age[41]: (a) Due to overall increased emotional regulation, older adults have lower reactivity to acute emotional stimuli; (b) Due to physiological and/or cognitive decline associated with aging, older adults may lose the intrinsic capacity to react or reappraisal as intensively as younger adults. While these theories provide informative descriptions of the potential processes associated with EWB in old age, there is a lack of understanding of the directionality/causality in the interactions between EWB and brain aging. Relying solely on human work, it is underdetermined if the level of EWB is a cause, byproduct, or consequence of certain intrinsic brain characteristics.[42,43] This lack of knowledge is in part due to the constraints in human studies for mechanistic research and interventions.

3 | ACTIONS AND BRAIN CIRCUITS OF EMOTIONAL PROCESSING IN NON-HUMAN ANIMALS, INCLUDING OLDER ANIMALS

Animal research offer several advantages for brain mechanistic studies. First, recent progress in optogenetic and chemogenetic tool development has offered ways to selectively label and manipulate specific neural circuits to determine their functional contributions.[44] Second, high-resolution brain imaging techniques in animals can provide cellular or subcellular level resolution, capturing the structure and activity of the fundamental units of nervous system.[45] Third, genetic models of aging-related diseases, such as Alzheimer's disease (AD), allow the study of pathological aging in animals.[46] Taken together, high-resolution brain imaging techniques and selective neural circuit manipulation strategies in animal models can identify the precise biological changes during typical and pathological brain aging and assess their contributions to emotional processing.

In human studies, self-report can provide direct access to subjective feelings and assessment of EWB, but in animal studies, other objective measurements are needed. It is worth pointing out that in certain non-verbal human populations, such as young children or older adults with speech impairment, assessment of emotional states and wellbeing must also rely on objective measurements. To study emotional processing across species, we instead adopt a theoretical framework that views emotions as central states of the brain that respond to affective stimuli and cause multiple cognitive, somatic, and behavioral changes.[22,47,48] Charles Darwin proposed long ago that an important function of emotion is to ensure the organisms to adapt to environmental

stimuli related to survival or reproduction.[49] Based on this functional consideration, objective measurements of the expressions of emotions have been developed across species. For animal studies, a dimensional view of emotions according to expression variations along several major axes such as valence, intensity, and persistence, has provided most traction to define emotion primitives and dissect underlying neural mechanisms.[50]

The evolutionary origin of emotion underlies the conservation of emotion processing circuits across mammalian species. For example, emotional valence includes both positive and negative components. A series of studies by Berridge and colleagues have identified conserved subcortical hedonic networks containing nucleus accumbens and ventral pallidum.[51,52] Neural activation of the hotspots in this network increases 'liking' reactions to pleasant stimuli. In terms of negative valence, neural circuits for fear and pain have been most intensively studied in animals. These studies have highlighted the key roles of amygdala circuits in fear learning and expression, which are mediated via downstream projections to hypothalamus and midbrain periaqueductal grey areas.[53,54] Furthermore, the subcortical circuits involved in affect reactivity have extensive, often reciprocal, interactions with a set of prefrontal cortical regions, including anterior cingulate, orbitofrontal, and insular cortices.[55–58]

Although the evolutionary expansion of the cerebral cortex in human appears to present a hurdle to study similar cortical networks of emotion regulation in experimental animals, recent developmental genetic and comparative neuroanatomical studies have suggested conserved topology of cortical networks for affect regulation.[59,60] If we stretch the cerebral cortex into a 2D sheet, its cellular architecture can be characterized by three concentric rings (Figure 1). The outer ring is composed of the hippocampus and olfactory cortex, and this allocortex has the simplest cell layer structure. The inner most ring circles the isocortex, which has the most elaborated cell layer structure and regulates sensorimotor functions for interacting with the external environment. The middle ring is named mesocortex and contains the regions implicated in emotion regulation, such as cingulate, orbitofrontal, and insular cortices. Furthermore, functional connectivity measures across species have identified three major cortical networks: DMN, VAN/salience network, and central executive networks.[61,62] Interestingly, the main connections in these networks follow distinct paths in the concentric ring cortical topology, with vmPFC serving as an overlapping node at the anterior end of the cortex and playing key roles in emotion regulation.[63,64]

Taken together, the vmPFC-inclusive cortical networks provide an extra layer of neural control over the subcortical circuits involved in affect reactivity. This layout suggests a nested network architecture with feedforward and feedback circuit loops to mediate the experienced and evaluative aspects of emotion processing.[63,65] Animal studies also provide a further insight that the cellular implementation of this network architecture is quite intricate. There are often distinct populations of neurons with different molecular signatures and anatomical connectivity patterns within the same brain areas. Opposing emotional expressions such as pleasure versus disgust, or fear versus desire, can be directly evoked from

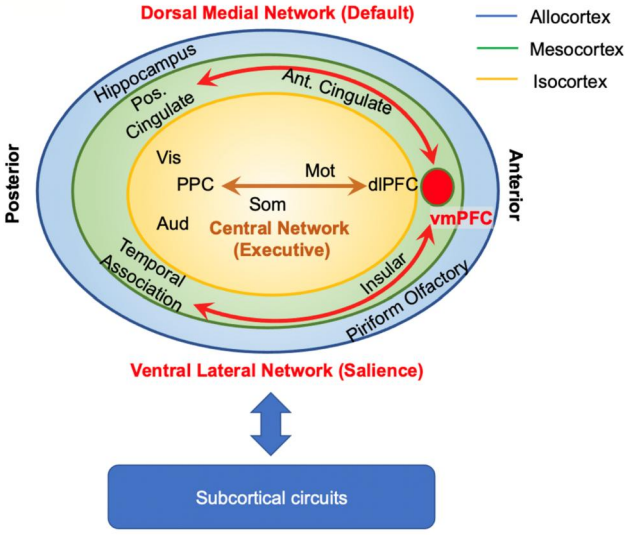

FIGURE 1 Cross-species comparable topology of brain cortical networks. Red indicates circuits supporting aging-related emotional processing.

neighboring or even intermixed neuronal populations in the same brain region.[66,67] How different neural representations are selected along the neuraxis of the nervous system to control appropriate emotion expressions is still incompletely understood.[68] Moreover, how aging affects the brain circuit architecture for emotion processing has not been investigated in depth.

4 | AN AGING-RELATED REACTIVITY AND REAPPRAISAL MODEL TO INFORM THE UNDERSTANDING OF EWB AND DEVIATION FROM EWB

Behaviorists and neuroscientists have had divergent views about how emotional stimuli evoke behavior and other responses across species. Behaviorists consider the behavior and other responses link stimuli and subjective feelings in human while neuroscientists consider the role of a central emotion state in further linking these pieces (stimuli, behavior and other responses, and subjective feelings).[22,47,48] By synthesizing principles from the two approaches, unique emotional processes involved in explaining EWB among TOAs, as well as emerging emotion processing circuits from animal studies, we here propose the importance of understanding the behavioral, psychophysiological, and neural processes of reactivity and reappraisal to emotional stimuli in capturing and differentiating evaluative and experienced EWB (Figure 2).

4.1 | Essential actions of the reactivity and reappraisal model

To ensure the comparability between human and animal, we simplify emotional stimuli based on the attributes, that is, degree of arousal

and valence, instead of content. Arousal and valence may be considered an immediate reactivity to stimuli from internal state in laboratory or real-world tasks. Many acute or chronic stressful events (e.g., retirement, caring for a loved one, loss of a loved one, relocation to senior living, etc.) and challenging tasks (e.g., taking life-long learning course, etc.) are incidents reflected in TOAs' moment-to-moment everyday life. But these events are not "emotional stimuli" themselves. We here argue that only with the arousal and valence components, a stimulus becomes affective. The perceived degree of arousal and valence can vary in TOAs based on past experience or the emotional regulation process, therefore, the relationship between perceived emotional stimuli and the emotional regulation process in TOAs are possibly bidirectional. Animal models allow direct experimental modulation of specific brain emotion processing circuits to determine the directionality/causality between the valence or arousal from affective stimuli and emotional regulation processes. Literatures on reactivity have been relatively consistent across species, including the importance of assessing behaviors (e.g., gaze, attention, facial expression, vocalization, etc.) and physiological responses (e.g., autonomic nervous system, inflammation, etc.). Conversely, there have been debates on formats of reappraisal. Here we emphasize the importance of additional processes following reactivity that regulate emotional status immediately or chronically (e.g., memory encoding and retrieval, cognitive control/inhibition, and semantic elaboration). The representativeness or reliability of animal behavioral paradigms in reflecting these reappraisal processes is controversial. We propose some potential compatible paradigms of reactivity and reappraisal across species (Table 2), but urge the animal research to invest on understanding these actions involved in reappraisal of valence and arousal related task stimuli.

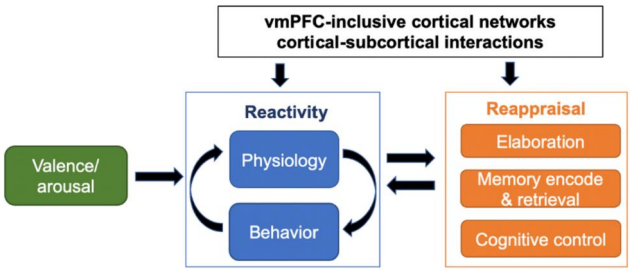

FIGURE 2 Reactivity and reappraisal model for understanding EWB in aging.

4.2 | Essential brain circuits of the reactivity and reappraisal model

Synthesizing human and animal literature on emotional processing, vmPFC-inclusive cortical networks regulate the reactivity, reappraisal, and their interaction in predicting EWB. vmPFC-centered cortical networks (i.e., VAN, DMN, FPCN) serve as hubs that play critical roles in regulating adaptive behaviors and functions (e.g., reappraisal, emotional regulation, physiological adaptation, etc.) that are essential components of reactivity or reappraisal.[69,70] Specifically, the VAN reorients attention in a contextually appropriate manner and inhibits habitual, maladaptive reactions; greater connectivity between VAN network and basal ganglia is related to better restraint of previously learned responses that are no longer appropriate.[71] Key regions of the DMN (i.e., vmPFC, posterior cingulate cortex, and precuneus) communicate with basal ganglia to support cognitive flexibility between existing stimulus associations and current behaviorally relevant stimuli.[72,73] FPCN is activated by a range of cognitive tasks, particularly those involving external attention and cognitive control. Activity in this network also scales with task difficulty suggesting a domain general role in effortful cognitive performance.[74] Meanwhile, vmPFC-centered cortical networks coordinate with selected subcortical networks, such as basal ganglia and thalamus, to regulate motivation and attention, and hypothalamus, amygdala, and other neuromodulator systems such as

TABLE 2 Proposed compatible behavioral and physiological paradigms of reactivity and reappraisal of emotional process across older adults and non-human animals.

Components	Human	Non-human animal
Affective stimuli		
• Positive	Smiling faces; positive word; happy life events	Social interaction; affiliative touch; food-reward association
• Negative	Sad faces; negative word; stressful or adverse life events	Fear conditioning; stress and pain
Reactivity	Gaze; attention; facial expression; autonomic nervous system changes	Facial expression; vocalization; gaze; pupil size; autonomic changes
Reappraisal		
• Semantic evaluation	Describe the feeling and insight toward emotional stimuli	N/A
• Memory encoding and retrieval	Encode and recall events that are emotionally relevant	Encode and recall fear or reward memories
• Cognitive control/ inhibition	Make decisions toward emotional stimuli	Fear extinction, reward devaluation

noradrenaline and acetylcholine systems for physiological reactivity.[75,76]

4.3 | Reactivity and reappraisal model in understanding and differentiating multi-dimensional composites of EWB

How do aging-associated reactivity and reappraisal changes, esp. in an acute, short-time frame, relate to evaluative (cumulative circumstances) versus experienced (single or repeated circumstance) EWB in old age? Or in other words, can we use a series of laboratory experiments on reactivity and reappraisal to reflect or predict a relatively longer term EWB? Reactivity to emotional stimuli directly participates in experienced EWB. Reactivity, by further processed with certain formats of reappraisal, also contributes to evaluative EWB. There are two types of timeframes that may explain how acute stimuli lead to chronic state of EWB: (a) repeated stimuli lead to an establishment of EWB; (b) acute stimuli with long-lasting effect that lead to a state of EWB. We propose that reactivity patterns as well as the sequential processes of reactivity and reappraisal can be used to predict the longer term EWB and differentiate aging-related changes in EWB.

5 | POTENTIAL APPLICATIONS AND REMAINING QUESTIONS OF THE REACTIVITY AND REAPPRAISAL MODEL FOR MODIFYING ANY DEVIATIONS FROM EWB

Neural circuit techniques have been widely applied to study brain developmental changes in younger animals and determine their functional relationships to affective behaviors. For example, it is known that fear extinction is impaired in adolescents.[77,78] Maturational changes in key affective regulation circuits centered around the medial prefrontal cortex have been linked to fear relapse in adolescents.[55,79] At a microscopic level, these maturational changes include excitatory-inhibitory balance, neuromodulatory inputs, and axonal myelination.[80,81] At a macroscopic level, maturation changes appear to progress in a cortical hierarchy from primary sensory and motor areas to paralimbic cortical association areas, including cingulate, medial prefrontal, orbitofrontal, insular cortices that are central to emotional processing and regulation.[82] Whether there is a relationship between maturation sequence and aging-related degeneration in the brain is an interesting open question. For example, are late maturing brain regions (such as paralimbic association cortices) subjected to early degeneration (last in, first out) or late degeneration (last in, last out)[82–84]? Moreover, it has been noted that the cellular pathology in age-related neurodegenerative disorders such AD propagates in paralimbic association cortical areas first, before extending to primary sensory and motor areas.[85,86] Although the underlying pathogenic mechanisms are not completely known, it could be hypothesized that the late maturation and enhanced plasticity of the paralimbic association cortical areas render them structurally less stable and more susceptible to cellular pathogenesis and socio-environmental risk factors accumulated through life experience,[59] leading to reduced EWB and mental disorders.

For individuals (those with pathological brain aging or younger adults) who have poor or abnormal evaluative or experienced EWB (e.g., anhedonia, loneliness),[43,52,87–92] domains of reactivity or the sequence of reactivity to various actions of reappraisal may be disrupted. Neuropsychiatric symptoms in pathological aging may be more relevant to a dysfunction of experienced EWB. Interventions may be informed by the reactivity and reappraisal model, including those targeting reactivity and reappraisal (e.g., selected mindfulness interventions, cognitive control training, biofeedback training, forming positive images), or brain stimulations (e.g., transcranial direct current stimulation, transcranial magnetic stimulation, deep brain stimulation) targeting specific brain regions or networks.

Another relevant question is on how pathological aging influences the role of reactivity and reappraisal in EWB. We previously found that a group with mild cognitive impairment had significantly decreased valence after mental challenge than typical older adults; increased quality of life was related to increased valence in the mild cognitive impairment group only; and strengthening vmPFC-inclusive cortical networks mediated the relationship between increased valence and increased quality of life across groups.[29] In a separate study, decreased vmPFC-inclusive cortical network and subcortical (amygdala) interaction to challenging tasks (where mild cognitive impairment had more decrease than TOAs) was related to decreased internal locus of control, the relationship of which was more evident in the patient group.[93]

6 | CONCLUSION

Within the umbrella of EWB research, the human work requires a better understanding of directionality between actions involved in emotional processing, as well as causality, including brain mechanisms underlying the actions of emotional processing and EWB. Mechanistic studies in animal models of normative and pathological aging can differentiate the correlative versus causative changes in emotional circuits and behaviors during aging. Once the relationships between age-related brain circuit changes and emotional states are determined in animal studies, the identified mechanisms may inform the directionality and specificity of age-related changes observed in human brain and emotional wellbeing. While modern technologies for circuit monitoring and manipulation have greatly advanced the dissection of emotion processing circuits in adult and developing animals, relatively few studies have applied such technologies to examine aging-related changes in specific emotion processing circuits and establish their causal contributions to changes in affect reactivity and reappraisal.[94–97] One of the

experimental challenges in animal studies is to establish robust measures of emotion expressions that can integrate a variety of objective indices such as facial expression, vocalization, motor reaction, autonomic and endocrine responses for tracking across age. Encouragingly, recent progress in automated data collection and machine-learning analyses offers new solutions to this challenge.[50] Thus, there are exciting research opportunities for using precise neurobehavioral measurements and causal circuit manipulations to establish the mechanistic links of brain aging to age-related changes in emotion processing. To close the loop in cross-species studies, human research may in turn inspire the development of animal models that go beyond emotional reactivity measurements and incorporate objective examination of the evaluative/reflective components of emotional wellbeing. Such components in animal behaviors may be found in ethologically relevant and enriched social environments.[98,99] Looking forward, although animal models would not capture the full spectrum of contents in EWB defined for humans, they hold the promise to complement the limitations of human work and offer mechanistic insights into the fundamental processes and neurobiological constraints of affect reactivity and reappraisal during aging.

KEYWORDS

aging, cross-species, emotional wellbeing, reactivity, reappraisal

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

There is no data presented in this paper.

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