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# A Homeostasis Breakdown Model of Subjective Cognitive Decline

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Abstract

Subjective Cognitive Decline (SCD) is a possible earliest detectable sign of dementia, but we do not know what mental processes lead to elevated concern. We summarize the previous literature on the biomarkers and functional neuroanatomy of SCD. To extend the current most-popular theory of SCD, compensatory hyperactivition, we introduce a new model: breakdown of homeostasis in the prediction error minimization system. A cognitive prediction error is a discrepancy between an implicit cognitive predictions and the corresponding outcome. Experiencing frequent prediction errors may be a primary source of elevated subjective concern. Our homeostasis breakdown model explains the progression both from normal cognition to SCD and from SCD to advanced dementia stages.

*Keywords*: subjective cognitive decline; preclinical dementia; fMRI; compensation

## Introduction

Subjective Cognitive Decline (SCD) refers to an individual's perception that their cognitive performance has declined, despite having no significant objective cognitive impairment. SCD may reflect one of the earliest signs of dementia, as it is a risk factor for developing mild cognitive impairment (MCI) and Alzheimer's Disease (AD) [1,2]. However, SCD is quite understudied -- which mental processes lead to SCD and the neural basis of SCD has yet to be understood. Here, we first provide a review of the current literature for biomarkers and functional neuroanatomy associated with SCD. Then, we will propose a new model that integrates existing findings in SCD into a new neural system dysfunction model, which involves heightened prediction error signaling and homeostasis breakdown.

## AD Biomarkers (neurodegenerative factors) and SCD

In order to investigate whether SCD represents a pre-clinical state of AD, the relationships between AD biomarkers in individuals with SCD were examined. In the traditional AD biomarker cascade, amyloid (Aβ) accumulation occurs prior to neurodegeneration and cognitive decline [3]. The most promising evidence that SCD precedes MCI and AD is that Aβ deposition is associated with SCD symptom severity but not with objective memory performance [4-6]. Vogel and colleagues [7] found that amyloid status predicted future cognitive decline (on average 4 years) among individuals with SCD. However, a larger longitudinal study [8] concluded that Aβ-status by itself does not predict the AD progression over a relatively brief time span of 2.5 years. More longitudinal studies are necessary to better understand the relationship between Aβ and objective cognitive decline in SCD. In addition to the accumulation of

amyloid plaques, AD is also associated with neurofibrillary tangles composed of tau protein. Tau accumulation is believed to be more closely related to neurodegeneration and cognitive decline in AD as compared with amyloid [9]. Tau is more associated with SCD, than with non-amnestic MCI [10]. Thus, like Aβ, the tau markers support the role SCD as an AD risk group.

Brain atrophy and white matter hyperintensities (WMH) have been also reported in SCD as seen in the early pre-clinical stages of AD progression. Several studies consistently reported cortical volume loss and thinning in the medial temporal regions in those with SCD [11-15], indicating the decreased structural integrity of memory system. Longitudinal observations also reported the association between atrophy and future cognitive decline in SCD [16,17]. The whole brain analysis by Verfaillie and colleagues [17] suggested that the steeper decline of cognition was not only associated with thinner cortex of the temporal region but also frontal and occipital cortices in SCD. Increased amounts of WMH in the widespread regions have also been reported in SCD [18,19]. These studies provide support for the idea that SCD may be an early transitional stage prior to the onset of dementia (i.e., MCI and AD), especially as seen with the perturbations in the memory systems.

**Functional Neuroanatomy and Compensation Theory in SCD**

The neural basis of elevated subjective concern for cognitive decline among older individuals with normal cognition is the least investigated but represents a growing area of research. Four fMRI studies investigated brain activation during memory-related tasks [20-23]. Most of these studies did not find group differences between participants with and without SCD in behavioral performance of the task, but they observed the

different functional brain activation patterns. The first study by Rodda and colleagues [23] measured brain activity while participants were encoding a list of semantically related words, which were later tested through a recognition paradigm. Whole brain analysis demonstrated increased activation in the lateral part of the prefrontal cortex (PFC) in those with SCD. The level of the PFC activation was positively correlated with task performance. The authors interpreted that increased PFC activation served as neural compensation for decreasing function of the primary hippocampal memory system. To test this compensation hypothesis, Erk et al. (2011) [20] investigated activation in the hippocampus and the PFC during memory encoding of faces and associated occupations through a region-of-interest (ROI) approach. Their results demonstrated decreased activation in the hippocampus and the increased activations in the dorsolateral PFC (dlPFC). Task performance positively correlated with dlPFC activation only in the SCD group, which provides support for the compensation hypothesis in SCD.

Hu et al. (2017) [22] utilized a task that emulated memory processes relevant to activities in daily life (future-oriented choice task). Brain activation was measured while participants were required to select an immediate or delayed reward regarding a personally relevant episodic future event. To successfully select the future-oriented choice (i.e., delayed reward) over the immediate reward, involvement of episodic memory and valuation system are crucial [24]. Unlike other studies, their study is the only one observed group differences in the task performance. The SCD group showed reduced preference for future-oriented choice, which has been previously demonstrated in those with MCI [25]. *A priori* ROI analysis showed that participants only in the control

group showed an association between greater hippocampal activation and more future-oriented choices. The whole brain analyses found reduced activation in medial frontal regions (medial frontal pole and ACC) and the insula in the SCD group, suggesting the diminished valuation function. The authors suggested that reduced involvement in the episodic memory and valuation system in SCD during decision-making process may reflect the attenuating attention and subjective evaluation system.

To address the possibility that increased PFC activation reflected general cognitive processes rather than only memory encoding, Hayes et al. (2017) [21] used an event-related design to compare brain activations for high-confidence successful recall versus failed recall. The SCD group showed increased activation for failed recall (i.e., negative subsequent memory) in the posterior areas (occipital, superior parietal, precuneus). They also regressed activation on a continuous SCD symptom severity to identify the neural correlates of SCD by combining participants in both groups. Participants with more severe SCD symptoms showed increased activation for failed recall in both frontal and posterior nodes of the default mode network (DMN), which is supposed to suppress its activities during cognitive tasks. They concluded that individuals with SCD rely on the altered neural system for successful memory encoding to maintain normal cognitive function.

Cognitive concerns in SCD mainly reflect perceived decline of memory function, but the other domains of cognitive function may also contribute to elevated concerns [26]. There are two fMRI studies with non-memory tasks. Dumas and colleagues [27] investigated the executive functioning in SCD by using the n-back working memory task. Although this study was limited to females (i.e., comparison between ones with

cognitive concerns and without concerns among postmenopausal women without hormone therapy), their study is the first to report the increased activation as increased cognitive load increased among those with SCD. These effects were found in the extended working memory system, including middle frontal (BA 9/10), ACC (BA 24/32), and precuneus (BA 13). Both groups showed the same level of behavioral performance. Another study in executive functioning by Rodda et al. (2011) [28] investigated activation during a divided attention task, where participants with SCD were required to respond to targeting stimuli while processing sequences of both visual and auditory information. Behavioral performance did not show group differences, but the SCD group demonstrated increased activation in two medial posterior regions: one in the cerebellum and another in thalamus extending to posterior cingulate cortex (PCC) and medial temporal lobe (hippocampus and parahippocampus). These two studies are consistent with the idea that early functional changes (i.e. increased activation) may manifest in SCD despite lack of impairment in behavioral performance or on the neuropsychological tests.

In summary, previous fMRI studies (Table 1) have suggested three neural phenomena in SCD: 1) loss of integration of memory system, 2) compensatory hyperactivation in the prefrontal cortex or use of other alternative neural resources to maintain normal performance, and 3) decreased prefrontal activation for subtle yet declining higher-order cognitive functions. In other words, the direction of neural activation (increased or decreased) observed in SCD depends on whether the expected level of performance can be maintained. To extend our understanding of functional neuroanatomy of SCD, more mechanistic and cohesive framework that can provide

explanations for dysfunctional processes is necessary, regardless the level of task performance or cognitive domain. Furthermore, it is not yet understood which specific cognitive processes rely upon compensation and how these processes are directly associated with SCD symptoms. As a potential framework or model to address these gaps in knowledge, we propose that disruption of prediction error minimization may underlie SCD symptoms.

**Background of Prediction Error Theory**

Our brain functions as a statistical optimization engine that constantly makes implicit predictions of sensory inputs [29,30]. That is, rather than passively receiving sensory information, it is actively making inferences. These inferences are propagated as predicted expectations to heteromodal association areas and the PFC. These expectations are compared with the current environment, and a behavior is chosen. Moreover, the difference between predicted and observed behavior is used as learning signal to adapt for better performance in the future. This constant process of comparing internally generated predictions with external reality is called “predictive coding” [31]. This is why we think of the brain as learning and adapting across all behaviors.

Prediction errors refer to the mismatch between the internally generated prediction and the external reality. The most prominent brain region that responds to such errors is the dorsal anterior cingulate (dACC). Both animal and human studies have demonstrated the increased activity in dACC to response to prediction errors [e.g., 32,33]. Similar terms for prediction errors are *conflict* [32,34] and *free-energy* [35]. Although there is a general consensus that dACC mediates error-related signals; neuroscientists have different opinions about the specific processes in the dACC and

the primary goal of the function [36]. Nonetheless (regardless the diverse terminology and theories of dACC function), the *minimization* of prediction error is a core organizing principal for computational function at the local neural circuit. This error minimization optimizes our internal predictions, which facilitates successful goal-directed behaviors and survival.

**Prediction error and SCD symptoms**

Suppose a man who is very experienced with a computer notices he's making more typing errors. If he experiences subtle yet frequent errors between his prediction ("I thought I typed out '*experience*'") and actual outcome ("I accidentally typed '*exp**ri**ence*'"), his level of SCD symptoms may rise. This type of error signal raises the activation in the dACC resulting in various level of awareness. We believe that an accumulation of implicit and subconscious sense of errors that they did not experience earlier in adulthood leads to the gradual more explicit level awareness of errors. Such awareness of errors could occur not only in memory, but rather across multiple cognitive domains, including attention, task switching, language, and mathematical operations.

Awareness of one's internal cognitive system is called metacognition. According to Nelson (1990) [37], metacognition has two primary operations: monitoring and control. Monitoring refers to the introspection of incoming sensory information and one's own performance, whereas control refers to an allocation of an action (i.e., self-regulation). These two operations are independent but reciprocally interacted. Both the prediction error [29,30] and conflict monitoring [32,34] frameworks provide mechanistic models for *monitoring* of errors or conflicts. These models, however, differ in the level of information processing they are meant to explain. Prediction error refers to the process

that can occur throughout the cortical network. Prediction errors provide a signal that our internal model need to be updated, and the signal is generated by distributed processes of our incoming sensory information [38]. These local prediction errors influence the local Hebbian learning model [39]. In this way, correct predictions are strengthened, and incorrect predictions are weakened [40]. On the other hand, conflict-monitoring framework refers to how the more extended controlled yet implicit cognitive process integrates generated error signals, such as prepotent response suppression. Unlike prediction error, which is general network learning signal, conflict monitoring refers to the specific monitoring and control functions in the dACC. The prediction error [29,30] process may specifically infer the earlier operation of *monitoring*, whereas conflict-monitoring [32,34] may associate with both *monitoring* and *control* operations suggested in the Nelson's framework [37].

In the framework of two operations of metacognition, SCD is an impairment of both: monitoring and early stage of control. Accumulated subjective experience of prediction errors or conflict-monitoring activities eventually construct the elevated self-awareness of cognitive decline. Experimental tasks which require to process implicit prediction errors and to suppress the inappropriate proponent response may be able to capture an early decline objectively in SCD. Furthermore, neuroimaging studies with these tasks will provide detailed neural mechanisms of dysfunctional metacognition in SCD.

**Prediction error and SCD characteristics**

Previous studies suggest that the cognitive implications of SCD symptoms depend on the level of education achievement [26]. Since higher level of education is

considered a marker of cognitive reserve, Stern [41,42] postulated that cognitive reserve provides resilience to neurodegeneration. Level of cognitive reserve may represent the sensitivity to prediction errors and utility of the error signals. Individuals with high cognitive reserve may be highly sensitive to prediction errors and interpret them as important learning signals to update the internal model. These individuals constitute a lifestyle of using these learning signals more frequently and effectively to make higher achievement, resulting in having high cognitive reserve.

Individuals with SCD are often highly anxious and characterized by their tendency to worry [1], usually expressed as high neuroticism in the Big Five personality trait model [43]. It has been demonstrated that individuals with high neuroticism are highly sensitive to prediction errors [44]. In the course of progression of neurodegeneration, these individuals may start noticing prediction errors earlier than those with low neuroticism. The frequent experience of errors may not only raise an awareness but may also elicit concern. Individual with high neuroticism may then interpret the perceived errors as important learning signals, resulting in symptoms of SCD.

The high prevalence of depressive symptoms is another characteristic that has been reported consistently in SCD [1]. Neuroticism is also highly associated with depression; however, the neuroticism and depressive symptoms may relate to the different aspects of SCD. Neuroticism may serve as a predictor of how an individual interprets perceived prediction errors, whereas depressive symptoms reflect the affective response to their interpretation of the prediction errors. Depressive symptoms in SCD, therefore, may be translated as a negative affective response (i.e., sad feeling)

to frequently experiencing errors (i.e., “monitoring” component of metacognition), leading to persistence of depressive mood over time [45]. Depressive symptoms may also be a form of adjustment disorder, where an individual may have an emotional reaction to their new experience of difficulty in both internal prediction and performance (i.e., “control” component of metacognition).

**Theories of the neural basis of SCD**

Compensatory hyperactivation of the prefrontal region is currently the most popular theory of the neural basis of SCD. Another theory is brain reserve [46], which proposes a structural basis for functional compensatory capacity. Alternatively, dedifferentiation [47], a loss of specialization of neural function resulting in diffuse brain activations, is theory which may explain hyperactivation in the prefrontal cortex. All of these versions of compensatory hyperactivation describe only the temporal transition from the pre-SCD state to the SCD state, and do not describe the dynamics of post-SCD neurodegeneration. Further, they do not describe how hyperactivation may contribute to post-SCD decline via harmful biological side-effects on the neural system such as neurotoxicity or excitotoxicity. For example, over-excited neuronal activities could promote neuronal cell death [48]. Here, we introduce homeostasis breakdown, a new mechanistic framework for comprehensive temporal dynamics in SCD and progression to AD.

**Homeostasis Breakdown**

Homeostasis -- or homeostatic regulation -- is the ability to maintain stability and equilibrium of the system. For example, the stability of our body temperature is a consequence of homeostatic processes that coordinate adjustments of muscles, blood

vessels, and sweat glands. When a cold environment decreases body temperature, the hypothalamus releases a signal to skeletal muscles promote shivering and a signal to blood vessels to increase resistance of blood flow (i.e., vasoconstriction). Both of these responses minimize heat loss from skin, helping to reverse the body's heat loss.

Compensatory hyperactivation may represent a homeostatic process that serves to maintain the stability of cognition in a changing neurobiological environment. We will use the temperature regulation example to illustrate where SCD fits in a homeostatic view of cognition. Homeostasis in cognition attempts to preserve cognitive function despite neurodegeneration, whereas the goal of temperature regulation is to maintain a fixed temperature against the surrounding air becoming colder. Neurodegeneration leads to prediction errors and corresponding SCD symptoms, much like the body temperature falling just enough to cause a sensation of coldness. Finally, the compensatory hyperactivation is the main homeostatic process that we are currently aware of in cognition, and this is analogous to the onset of vasoconstriction of blood vessels to prevent hypothermia.

Homeostatic processes can have negative side effects. Extreme vasoconstriction for an extended period of time can lead to vascular cell loss. Similarly, compensatory hyperactivation tends to overwork the neural system (i.e., glutaminergic excitotoxicity), and there is evidence that this can lead to neuronal death or production of Aβ [49]. Thus, although homeostasis can slow the onset of cognitive decline, this may come at the cost of negative side effects that weaken the core cognitive infrastructure. This may explain why individuals with SCD tend to experience a relatively rapid decline into AD [50].

**Future Directions**

Clinicians do not yet have a standard intervention protocol for individuals with SCD. If more details of cognitive processes and the neural basis for SCD were understood, an effective intervention may be developed. A recent meta-analysis of experimental interventions for SCD suggested that cognitive restructuring therapies may improve metacognition (i.e., alleviate self-perceived cognitive challenges) [51], indicating that SCD could be a modifiable risk factor of dementia. Alleviating SCD symptoms along with associated psychological distress may slow neurodegeneration, such as atrophy and Aβ accumulation, by reducing hyperactivation. More studies investigating markers of neurotoxicity in SCD are necessary to provide basic evidence for psychotherapeutic interventions in the earliest stages of dementia.

**Conclusions**

In common scientific practice, the term *subjective* may generally be disfavored because it connotes *a lack of objectivity*. The self-assessments used to diagnose SCD presumably include individual biases. However, they appear to comprise valuable information such as cognitive decline over time and underlying neurophysiological pathologies. More studies and theoretical frameworks that can comprehensively explain temporal dynamics including the positive and negative by-products of compensatory hyperactivation are necessary. In this review, we proposed that prediction error, a metacognitive process, potentially leads to SCD symptoms. We also introduced homeostatic breakdown as a new framework that incorporates and integrates the current findings with the new prediction error perspective to describe the cascading effect of neurodegeneration and cognitive decline in SCD. This framework has the

potential to motivate new standard therapies for SCD that focus on alleviating not only the subjective symptoms but also slow progression of dementia due to neurotoxicity from compensatory hyperactivation.

Table 1

*Summary of fMRI studies in SCD*

| **Authors & Year** | **Type of task** | **Participants** | **Hyperactivation** (SCD > Control) or positive correlation with SCD symptoms | **Hypoacitivation** (Control > SCD) or negative correlation with SCD symptoms | **Behavioral Performance** |
|---|---|---|---|---|---|
| Rodda et al. (2009) | Memory encoding | 10 memory clinic SCD vs. 10 Controls (age: 64.2 vs. 68.0) | L PFC (BA6/9/44/46) | | 1) No group difference in behavioral performance<br>2) Positive correlation between PFC activation and recognition performance in both groups. |
| Erk et al. (2011) | Memory (encoding, recall, recognition) and Working memory (n-back) | 19 memory clinic SCD vs. 20 Controls (age: 68.4 vs. 66.8) | R DLPFC during recall (ROI analysis)<br><br>*no group difference during encoding, recognition, n-back | Hippocampus during recall (ROI analysis) | 1) No group difference in behavioral performance<br>2) Positive correlation between DLPFC activation and recognition performance in SCD.<br>3) Positive correlation between hippocampal activation and recognition performance in Controls |
| Hayes et al. (2017) | Memory: successful vs. unsuccessful encoding | 23 SCD vs. 41 Controls (age: 68.6 vs. 67.5)<br>* 21 out of 23 were memory clinic SCD | 1) Negative subsequent memory effect in Occipital lobe, SPL, PCC<br>2) More complains, more negative subsequence memory effect in DMN (PCC, precuneus, VMPFC) | | No group difference in behavioral performance |
| Hu et al. (2017) | Future-oriented decision making | 20 memory clinic SCD vs. 24 Controls (age: 68.3 vs 66.49) | | 1) Medial frontal polar cortex, ACC, Insula, | 1) SCD showed reduced future-oriented choices<br>2) Positive correlation between hippocampal activation (ROI analysis) and future-oriented choice in only Control. |

| | | | | | |
|---|---|---|---|---|---|
| Dumas et al. (2013) | Working memory (n-back) | Postmenopausal women: 12 cognitive complainers vs. 11 controls (age = 56.8 vs. 57.1) | MFG (BA10/9), ACC (BA24/32), insula (BA 13), precuneus (increased activation as WM demand increased) | Caudate | No group difference in behavioral performance |
| Rodda et al. (2011) | Divided attention | 11 memory clinic SCD vs. 10 Controls (age: 64.6 vs. 68.0) | L medial temporal, bilateral thalamus, PCC, caudate | | No group difference in behavioral performance |

*Abbreviations*: SCD: subjective cognitive decline, PFC: prefrontal cortex, BA: Brodmann area, DLPFC: dorsolateral prefrontal cortex, ROI: region-of-interest, SPL: superior parietal lobe, PCC: posterior cingulate cortex, DMN: default mode network, VMPFC: ventmedial prefrontal cortex, ACC: anterior cingulate cortex, MFG: middle frontal gyrus, WM: working memory.

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