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Hypothesis

Cognitive Debt and Alzheimer's Disease

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Abstract. We propose the concept of Cognitive Debt to characterize thoughts and behaviors that increase vulnerability to symptomatic Alzheimer's disease (AD). Evidence indicates that depression, anxiety, sleep disorder, neuroticism, life stress, and post-traumatic stress disorder increase risk for AD, and we suggest they do so by increasing Cognitive Debt. Repetitive negative thinking (RNT), a behaviorally measurable process common to these factors, may drive Cognitive Debt acquisition. RNT transcends disorder-specific definition, encompasses rumination and worry, and is defined by perseverative, negative thought tendencies. Evidence of dysregulated stress responses supports the concept of Cognitive Debt, of RNT as its causal mechanism, and of an interaction with the APOE-ε4 genotype to increase vulnerability to clinical AD, independent from traditional AD pathology. Defining a more specific behavioral profile of risk would enable interventions to be targeted earlier and more precisely at individuals most vulnerable to developing AD. Additionally, modulating RNT could potentially reduce risk of clinical AD. Interventions to reduce RNT are discussed, as are suggestions for future research. For these reasons we submit that the Cognitive Debt model may aid understanding of the psychological mechanisms that potentially increase predisposition to AD.

Keywords: Alzheimer's disease, anxiety, APOE, cognitive reserve, depression, mindfulness, neuroticism, PTSD, sleep, stress

INTRODUCTION

Yaakov Stern introduced the concept of cognitive reserve [1, 2] to describe a constellation of psychological engagements that confer relative protection against cognitive decline and clinical Alzheimer's disease (AD). Education [3], social networks [4], and the personality characteristic 'conscientiousness' [5] are among the lifelong factors shown to increase reserve. In this article, we propose that engagement in certain cognitive processes actively depletes reserves so much so that vulnerability to the pathologic effects of AD increases—such activity accrues Cognitive Debt. Similar to the independence of positive and negative emotions [6], Cognitive Debt does not exist on the same axes as those proposed for cognitive reserve (e.g., not simply low educational attainment, social isolation, etc.). Pooling the literature, we have identified clinical symptoms, personality traits, and life experiences that increase Cognitive Debt. Further, we highlight a modifiable cognitive process, repetitive negative thinking (RNT), that appears to underlie these factors.

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COGNITIVE DEBT FACTORS

Depression

An extensive literature supports the association between depression and AD [7]. Studies report late-onset depression as a prodromal feature of AD risk [8] and also earlier-life depression as a risk for AD. A review by Byers and Yaffe [9] found stronger evidence in favor of an earlier-life depression association with AD risk; however it is likely that depression may be both a risk and a prodromal symptom. Depressed middle-aged and older adults exhibit steeper cognitive decline [10], and two systematic review/meta-analyses

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showed compelling evidence that history of depression significantly increases risk of AD [11, 12]. Increasing number and severity of depressive episodes are associated with greatest risk of AD [13, 14]. Additionally, a longer interval between diagnosis of depression and later AD diagnosis has been associated with greater AD risk [12], findings that further implicate depression as a premorbid risk for AD more so than a prodromal symptom.

In non-clinical populations, depressive symptoms also increase risk of AD [15] with each additional symptom increasing risk by approximately 20% [16]. Cognitive dysfunction associated with depression is even evident in young adults [17]; whether this relationship indicates risk for AD in specific individuals in later life has not yet been investigated.

Anxiety

Less is known about the influence of anxiety on AD risk despite its high occurrence in the general population [18], in AD [19], and frequent co-morbidity with depression [20]. Results thus far broadly suggest anxiety symptoms are associated with cognitive impairment [21–24], risk for dementia [22, 25, 26], and conversion from mild cognitive impairment (MCI) to AD [27] in older age; although no relationship [28, 29] or reduced short-term and increased long-term AD risk [30] have also been found. Measurement type, follow-up period, and drop-out rates differed considerably between studies; yet these findings do suggest a relationship between anxiety (even in individuals without clinically significant symptoms), memory, and AD.

Sleep disorder

Sleep disorder, marked by insomnia, difficulty initiating and maintaining sleep, and daytime sleepiness is a common psychological health issue and highly prevalent in older adults [31]. It is also associated with cognitive impairment [32–34], and increased risk of cognitive decline [35–37], MCI [38], and AD [38–40]. Episodic memory is generally affected early in AD and is particularly vulnerable to sleep loss [40]. Indeed, learning and episodic memory retention deficits are evident following acute and chronic sleep deprivation [41]. It has been suggested that increased risk of clinical and pathological AD may be among the long-term consequences of sleep disorder [39, 42] (Annex 1).

Neuroticism

The personality trait, neuroticism, typified by negative affectivity and proneness to distress [43], has been consistently implicated in risk for AD. In non-demented older adults, neuroticism is associated with worse cognitive function [5, 44] and steeper rate of cognitive decline [5, 43, 45–47], independent of depressive symptoms [44–46]. Prospective studies indicate increased risk of MCI [48] and AD [45, 46, 49]. Two recent systematic reviews/meta-analyses supported a role for neuroticism in increased risk of dementia [50, 51]. The specific characteristics of neuroticism, 'anxiety', 'depression', 'angry hostility', and 'vulnerability to stress', were the strongest predictors of conversion to AD and cognitive decline [51, 52].

Life stress

Early life stressors have a profound impact on dementia risk [53, 54]. Investigators from the Cache County Memory Study found that maternal death during adolescence was associated with a greater than 2-fold increased risk of AD [55]. Indeed, early life stress has a negative impact on memory, executive function, and global cognitive function that extends into adulthood, with impairments becoming more profound with increasing chronicity of the stressor [56]. In a 35-year prospective study of women, mid-life experience of frequent/constant psychological stress was associated with increased risk of AD [57]. Additionally, high job strain (low control/high demand) increases AD risk [58]. This increase may be due to *perception* of stress rather than objective encounters with stressors, because a 30-year longitudinal study found that reactivity to stress drove the association with AD, and not work-related stress itself [59].

Post-traumatic stress disorder

Post-traumatic stress disorder (PTSD) encompasses the categories of anxiety disorder and life stress, therefore an association with increased AD risk might be expected. A small body of research has explored its relationship with cognition and dementia. Combat veterans with a history of PTSD show a near two-fold increased risk of dementia and AD [60, 61], even after accounting for other comorbidities and level of combat exposure [60].

Cognitively, a recent meta-analysis of six samples showed that older adults with PTSD (either combat veterans or Holocaust survivors) showed greater impairment relative to either trauma-exposed non-PTSD groups or healthy controls [62]. The authors noted that the number of studies and their sample sizes were small and that possible confounds (including

pre-morbid IQ) were not well addressed; however, the results consistently revealed global cognitive impairment, with learning and memory most profoundly affected.

Inter-relation

We propose that depression, anxiety, sleep disorder, neuroticism, life stress, and PTSD are proxies for Cognitive Debt. While the existing literature on most of these factors is limited, the available findings do suggest that each impairs cognition and increases AD risk, and all show a high degree of inter-relation. Anxiety and depression often occur together [20], and both feature in neuroticism [63, 64]. Neuroticism is also associated with greater risk of PTSD following trauma [65]. Childhood adversity is associated with increased risk of neuroticism [66] and symptoms of anxiety, depression, and affective disorder that extend into mid-life [67]. In adulthood, sleep disturbance is frequently comorbid with depression, anxiety, and PTSD [68, 69]. The effect of mid-life stress exposure on personality has been inconsistent [70]; however when Löckenhoff et al. [71] selected experiences of extremely adverse life events in an 8-year longitudinal study, they found increases in neuroticism, independent of baseline personality.

The single largest predictor of psychiatric disorder in adults is presence of psychiatric symptoms in childhood and adolescence [72], indicating that barring any significant negative life event, psychiatric profile is relatively established by the end of young-adulthood.

A shared maintaining process?

Are the relationships between factors of Cognitive Debt due to a shared maintaining process, a common vulnerability, consequences of undetected disease pathology, or an as yet unknown factor? Monozygotic twin studies suggest that while genetic vulnerability to neuropsychiatric disorders exists [73], environmental factors are also strongly influential [74]. An integrated view of these Cognitive Debt risk factors may clarify their high comorbidity [75], therefore we turn to the transdiagnostic literature to consider a shared psychological mechanism.

REPETITIVE NEGATIVE THINKING

Clinical and cognitive psychologists independently identified a common process that underlies the factors outlined above. RNT, defined as self-relevant, persistent thoughts that elaborate on negative themes [75, 76] and Perseverative Cognition, defined as repetitive, perseverative activation of cognitive representations of previous or anticipated stressful events [77], both describe a transdiagnostic process. RNT and Perseverative Cognition broadly encompass future-directed (worry) and past-directed (rumination) negative thoughts, describe the thought process rather than the time-orientation or content [78], and define a relatively stable style of thinking [79]. Both definitions maintain that this process can be triggered by external or internal events and can be sustained outside of conscious awareness [77, 80]. Given the analogous definitions and descriptions of these terms, we prefer to use RNT, however as the majority of the research has been conducted following the disorder-specific tradition, we summarize findings primarily using the terms 'rumination' and 'worry', but emphasize that the *process* being described, RNT, underlies both [76, 81].

RNT and cognitive debt

As reviewed earlier, recurrent depression is linked with increased risk of AD [13], and a ruminative response style is believed to be a perpetuating factor of depression because it predicts symptom onset, duration, and number of depressive episodes in clinical and non-clinical adult populations [79, 82–84]. Rumination in adolescence is associated with greater risk of depressive episodes in adulthood [85], and mediates the relationship between neuroticism, anxiety, and depression in healthy, at-risk, and depressed adolescents and adults [86–88]. It is also a feature of neuroticism [82]. In prospective longitudinal studies, prior rumination predicted onset of PTSD symptoms after an earthquake [89] and contributed to maintenance of PTSD symptoms up to three years after a traumatic event [90–92]. In clinically anxious individuals, those with excessive worry had earlier onset of symptoms, longer duration, and greater symptom severity than non-worriers [93]. Furthermore, a substantial body of literature supports worry and rumination as maintaining factors in disrupted objective and subjective measures of sleep [94, 95].

RNT and healthy populations

Considerable evidence suggests that clinically healthy individuals also engage in worry and rumination [96, 97], albeit to a lesser extent. Even in this population rumination and worry are associated with negative affect [78] and predict symptoms of

depression and anxiety [98, 99]. Experience of stressful events predicts increased rumination in adolescents and adults [100], and rumination appears to mediate the relationship between stressful life events and subsequent negative affect [100, 101]. Indeed, experimentally inducing rumination and/or worry prolongs both depressed and anxious mood [102, 103] and sleep disruption [95] in non-clinical populations.

RNT and cognition

In a comprehensive review examining the relationship between rumination and cognitive processes, Whitmer and Gotlib [104] concluded that state and trait rumination in clinical and non-clinical samples were associated with difficulty in disengaging from or forgetting previously relevant information and updating stored information in tasks of working memory and long-term memory. They suggested that impairments attributable to active (state) rumination were due to diversion of finite cognitive resources away from task-relevant processing, and trait rumination was better explained by a chronic narrowing of attentional scope, resulting in a limited set of thoughts immediately available (i.e., from working memory) or accessible (i.e., from long term memory). Indeed, in a 15-month longitudinal study, rumination predicted decreases in selective, but not sustained, attention [105], supporting the idea that it is the disengagement and selective reengagement of attention that is most impaired by RNT.

From a psychological viewpoint, we propose that RNT increases Cognitive Debt, possibly through a process that chronically narrows attention and diverts cognitive and emotional resources to distressing thought processes. (See Annex 2 for discussion of therapies targeting RNT).

STRESS

A shared vulnerability

Psychological stress arises when the challenge presented exceeds an individual's ability to cope [106]. In addition to sharing RNT, the factors of Cognitive Debt are also associated with disordered physiological and subjective experience of stress: depression [107], anxiety [108], insomnia [109], neuroticism [110, 111], PTSD [112], and life stress [113]. Indeed, RNT itself is associated with elevated stress hormones and is believed to be a marker of chronic stress [114, 115]. While the majority of stress research has focused on proximal consequences of a stressor, Brosschot and colleagues [114] comment that it may be the prolonged physiological activation more distal to the stressor (or even the idea of a stressor) that has the most profound impact on disease. It is possible that engaging in RNT, a relatively automatic process that can occur outside of conscious awareness [77], may over the course of a lifetime, chronically activate the stress response, increasing vulnerability to insult and toxicity. Just as cognitive reserve in older adults may be conceptualized as a proxy for the brain's cumulative engagement in stimulation [116], Cognitive Debt could be seen as an indicator of cumulative exposure to distress.

The HPA axis

The physiological cascade of the stress response has been described in detail elsewhere [117]. Briefly, perception of stress activates the hypothalamic-pituitary-adrenal (HPA) axis, by initiating hypothalamic secretion of adrenocorticotrophic hormone-releasing factor, causing pituitary secretion of adrenocorticotrophic hormone, and finally adrenal release of glucocorticoids (primarily cortisol in humans). Cortisol binds preferentially to neurons in the prefrontal cortex (PFC), hippocampus, amygdala, and other limbic structures [118]. While the amygdala activates the HPA axis, the PFC and hippocampus regulate it via negative feedback circuits [118]. Activity within the hippocampus, amygdala, and PFC (specifically orbitofrontal) is related to factors of Cognitive Debt [73, 119–122], and these regions are functionally responsive to stress [123]. Independent from clinical disorders, the amygdala, orbitofrontal PFC, and hippocampus are implicated in mood regulation and cognition [124]. Acute stress reactions are evolutionarily adaptive responses to danger, promote allostasis [125], and in fact benefit function in certain cognitive domains. Sustained stress and/or dysregulated HPA axis function, however, have been associated with increased allostatic load (i.e., physiological deterioration) [125], cognitive impairment and decline [126, 127], and AD [128]. Indeed, several models have been proposed linking depression with increased risk of AD via HPA-axis dysfunction [9, 129, 130].

Theories of stress

The prevailing "Glucocorticoid Cascade Hypothesis" posits that glucocorticoids become neurotoxic after their prolonged elevation, potentially reducing the brain's capacity to endure neurological insults [131], and consequently increasing risk for AD. Swaab

et al. [132] suggest an alternative explanation—that the ongoing progression of AD pathology causes both HPA axis dysregulation and impaired cognition. The two hypotheses may both be true. Put into the context of the psychological evidence outlined earlier, a ruminative cognitive style (associated with increased HPA axis activation) develops in adolescence, is influenced by life events, and increases vulnerability to clinical disorders, which may in turn increase risk for AD; additionally progression of AD pathology may exacerbate this vulnerability leading to even greater HPA axis dysregulation and decline. It is unlikely that the proposal put forward by Swaab and colleagues exists in isolation, for if one were to reconcile the psychological literature with their proposal, this would suggest that pathological AD commences at or before adolescence, when an individual's psychiatric profile is consolidated. At present no evidence exists to suggest that the inception of AD pathology begins this early.

In addition to glucocorticoid release, the pathophysiological sequelae of chronic stress (and by implication, RNT) also include elevated burden on the vascular system and increased neuroinflammatory response, both of which have been linked to factors of Cognitive Debt and are being investigated as causally involved in AD [133–135]. Additionally, failure to activate the repressor element 1-silencing transcription factor (REST), a regulator of the brain's stress response, has been associated with cognitive impairment and AD [136]. Whether reduced REST activation is a result of chronic stress has yet to be determined, however represents a promising line of research. The relationship between Cognitive Debt and amyloid-β (Aβ) and neurofibrillary tangles, hallmark pathological features of AD, is not conclusive (See Annex 1 for further discussion).

APOE: EPIGENETICS

From an epigenetic perspective, both genetics and lifestyle are believed to influence development of clinical AD, therefore we explore this interaction using Cognitive Debt and the APOE gene. Based on the model, we would expect an additive effect of Cognitive Debt and genetic risk on AD risk.

The APOE gene expresses the ApoE protein, which is implicated in a number of neurobiological roles [137], and in humans, exists as three common variants (ε2, ε3, ε4). The ε4 allele delivers the greatest known genetic risk for sporadic AD [138], however because ε4-allele possession is not deterministic, lifestyle is one possible mediator of its effect. ε4 carriers show worse recovery following physical insult to the brain such as traumatic brain injury [139], and here we show that psychological insults (i.e., stress and factors of Cognitive Debt) interact with APOE.

In the central nervous system, the ApoE protein is normally expressed by glia, but in reaction to injury [140] or excitotoxic stress [141] neurons also release ApoE. Neuronally expressed ApoE4 is most susceptible to fragmentation, and these fragments lead to a constellation of detrimental events, which include neuronal damage, tau phosphorylation, neurofibrillary tangle formation, mitochondrial dysfunction, and GABAergic interneuron impairment [137]. As evidence of their association with injury, brains of AD patients contain higher quantities of these fragments than matched controls [142]. These molecular findings help explain why the prognosis for ε4-carriers following injury is worse than for non-carriers; and why psychologically-initiated stress may also be damaging for ε4-carriers, especially because neurons treated with an excitotoxic stressor have even higher mortality under conditions of elevated glucocorticoids [143]. Human literature examining interactions with APOE are limited, but preliminary findings appear to support these data.

Depression and APOE

Longitudinal studies have shown an additive negative effect of ε4-genotype and depression on cognitive function [144], cognitive decline [145], and conversion to MCI [146] and dementia [147, 148]. Indeed, two separate studies showed that ε4-carriers with depression had a greater than 7-fold increased risk of dementia or AD compared with those who had neither risk factor [149, 150].

Anxiety and APOE

To our knowledge, no longitudinal study has examined the interaction between APOE and anxiety on cognitive decline, or risk of MCI or AD. Two cross-sectional studies employing middle-aged adults (50–66 years) showed that non-pathological state and trait anxiety were associated with worse executive functioning in homozygotic ε4-carriers, with a trend evident in heterozygotes [151, 152].

Sleep and APOE

To our knowledge only one study has investigated the interaction between sleep disturbance, APOE, and AD. In older adults followed for up to 6 years, better sleep quality (measured by wrist movement during

sleep) attenuated the ε4-related risk of incident AD by approximately 50% [153]. The data also indicated that sleep consolidation was independent from the APOE risk causal pathway.

Neuroticism and APOE

To date two studies have examined the relationship between neuroticism and APOE. In a study of 597 older adults (mean age = 78.6 years), neuroticism was negatively correlated with global cognition in ε4-carriers, and the ε4-related risk of AD was even greater in individuals with high neuroticism [154]. A separate study found no interaction between neuroticism and APOE in terms of AD risk [51]. The latter study included significantly younger participants (mean age = 56.5 years) and had a smaller percentage of AD-conversions (5.4% versus 14.3%), which might explain the discrepant findings.

Life stress and APOE

A number of studies have investigated genotype differences in response to life stress. When exploring self-reported health of earthquake survivors, ε4-carriers with high subjective or objective exposure reported worse health, feeling less in control, and a marginally greater likelihood of depression and difficulty with daily activities compared to those with low exposure [155]. Level of exposure did not have health consequences for non-carriers. Indeed, the influence of increasing number of objective stressors on self-reported health also appears to be mediated by APOE genotype [156], with objective stressors reportedly increasing perceived stress in ε4-carriers by 347–531% [157]. Feelings of stress have also been associated with greater depressive symptoms in ε4-carriers [158].

The poor response of ε4-carriers to stress and adverse events extends into cognitive function. Middle-aged and older adult ε4-carriers' cognitive performance declined with increasing number [159] and severity [160] of negative life events. ε4-carriers with increasing psychosocial stress demonstrated reduced cognitive performance compared with non-carriers or those with lower stress [161, 162]. Even early life stress has been associated with significantly greater later-life decline in ε4-carriers [163], although this finding has not been reliably replicated [55].

PTSD and APOE

To our knowledge no study has yet examined the possible interactive effects of APOE and PTSD on health or cognition.

Cognition and APOE

The precise neuropsychological consequences of the interactive effect of Cognitive Debt and APOE on cognition have not been consistent across studies: global cognition [144, 145], memory [160, 162, 164], executive function [151, 152, 161], visuoconstruction [161, 164], language [164], and processing speed [159, 161] have all been reportedly affected. Some studies used a battery of tests and only found selective differences while others only reported data from a single domain. It is clear that more research will need to be conducted to disambiguate these findings. Importantly, in all studies cited, measured performance was equivalent for both ε4-carriers and non-carriers in the absence of trauma or stress.

HPA axis and APOE

Few studies have explicitly examined the association between APOE and the HPA axis on cognitive function. Cross-sectional studies have shown an interactive effect of genotype and cortisol levels on cognition—ε4-carriers with either higher waking or overall cortisol levels performed the worst [162, 164]. Longitudinal studies report conflicting results. In one study lower morning, higher evening, and flattened diurnal variability of cortisol levels were associated with memory decline, solely in ε4-carriers [165]. Another study that examined two distinct cohorts found an ε4-related difference in cortisol levels in the first year of the study, but not in subsequent years, and showed no relationship between cortisol, APOE, and cognition [166]. Variation in cortisol measurement methods might explain these inconsistencies: time of day/season, source (urine, saliva, blood, cerebrospinal fluid), and study conditions are all variables that are not reliably considered or controlled in the literature [112, 167], therefore results across studies need to be compared with caution.

APOE summary

Many of the studies examining the interaction with APOE were conducted with older adults, therefore may have been affected by prodromal dementia (i.e., AD pathology) because Aβ is believed to accumulate decades before symptom onset and even earlier in ε4 carriers [168], and is associated with cognitive deficits [169]. More studies with younger adults would help disambiguate direct gene effects from those related to AD pathology [170]. Likewise, studies using consistent methods of cortisol measurement that explore

whether ε4-carriers show elevated or aberrant cortisol levels under normal conditions, or whether differences emerge in response to stress could help resolve the discrepancies in the literature. Rather than promoting a model where ε4 genotype instigates worse function *per se*, the literature suggests that stress and trauma are particularly detrimental to ε4 carriers. Acknowledging the limitations and the small amount of data, there is preliminary indication of an additive negative effect of Cognitive Debt on ε4-related risk for AD.

DISCUSSION

In this article, we propose the concept of Cognitive Debt to explain how depression, anxiety, sleep disorder, neuroticism, life stress, and PTSD all appear to increase risk for symptomatic AD, and how the ε4 genotype may interact with these factors to increase risk. These proxies for Cognitive Debt are marked by abnormal responses to stress, and it is plausible that over the course of a lifetime, early and persistent exposure and/or maladaptive responses to stress increase risk of cognitive decline and clinical AD. The neurobiological signature of Cognitive Debt and AD might emerge from the relationship between the hippocampus, PFC, and amygdala, and the HPA stress response. Indeed the link between depression, the HPA-axis and reduced cognitive reserve on risk for AD already exists in the literature [130]. We extend this argument by incorporating other psychological factors, highlighting their inter-relatedness and introducing the concept of Cognitive Debt to indicate that these factors may actively deplete cognitive resources. We suggest that RNT is a behavioral manifestation of Cognitive Debt, which can be initiated and maintained without external trigger or conscious awareness, and can drive allostatic overload. RNT diverts cognitive resources and narrows attentional scope toward repeated activations of negative thoughts, thus provoking the opportunity to repeatedly experience physiological and psychological distress. Non-clinical individuals also engage in this style of thinking with detrimental consequences, which is important to note because not everyone who develops AD has a clinical history.

The limitations of the model must be acknowledged. We have suggested this testable concept of Cognitive Debt, but it has not yet been empirically validated, additionally no evidence yet exists regarding the long-term impact of RNT on neurodegeneration or AD risk. Cognitive Debt accumulation may not be restricted to AD, rather it may be linked with cognitive impairment more generally (e.g., the repeated distressing cognitions experienced in schizophrenia could play a causal role in the disorder's association with cognitive impairment). Likewise, the specificity of RNT to factors of Cognitive Debt is not yet clear. RNT is also a feature of other disorders (e.g., obsessive compulsive disorder, autism spectrum disorders), and to our knowledge no study has directly investigated their relationship with AD risk. Additionally, we have used the terms rumination and RNT broadly, however contained within them there are different types (e.g., depressive, angry) and subtypes (e.g., reflective, brooding) [171]. There are currently not enough data to determine which, if any, may be most damaging. Beyond RNT, there are additional transdiagnostic processes that may increase vulnerability, such as thought suppression [75]; however we decided to implicate RNT as it has the strongest evidence base and theoretical support for an association with AD. Finally, enthusiasm for these associations must be tempered by recognition that relatively few studies have examined these relationships and many are in need of replication.

Considering factors that contribute to cognitive reserve and Cognitive Debt may help explain the frequent discrepancy between pathological and symptomatic AD [2]. Individuals with high reserve and low debt might remain clinically healthy despite aggregation of AD pathology [172]; likewise those with low reserve and high debt might be at greatest risk for clinical AD. Combining these psychological characteristics with advanced knowledge of physical risks (e.g., inactivity, diabetes), neuroimaging techniques (e.g., Aβ and tau imaging), and genetic data (e.g., APOE, TREM2) would allow development of a more complete profile to identify those at greatest risk for AD. If future research supports RNT as a significant predictor of, and contributing factor for, AD then interventions to reduce RNT could be introduced to particularly vulnerable populations (i.e., those with Cognitive Debt and/or ε4-genotype). These interventions could be offered at an early age to help shape the course of cognitive-behavioral style. If effective, such interventions could significantly impact public health by reducing risk for AD and other adverse health outcomes.

ANNEX 1: AD Pathology

Aβ is believed to preferentially accumulate in brain regions of continuous elevated activation [173], beginning in the orbitofrontal cortex, amygdala, hippocampus, before spreading to other regions [174].

Remarkably, these inception points all have high glucocorticoid receptor density [118]. Indeed evidence from the animal and cellular literature suggests that stress and glucocorticoids contribute to both Aβ and tau pathogenesis, particularly in the hippocampus and PFC [175, 176]. Therefore Cognitive Debt might be associated with greater AD pathology. Extending the concept of cognitive reserve (that for a given level of function individuals with high reserve can sustain more pathology than those with low reserve [2]), one might expect the inverse relationship in Cognitive Debt: lower AD pathology at a given level of function or worse cognitive function at a given level of pathology. Combining these hypotheses we would predict that factors of Cognitive Debt would be associated with greater AD pathology, which would in turn be associated with worse cognitive function than matched-controls. This prediction is partially supported.

In depression, the serum $A\beta_{40/42}$ ratio (a peripheral marker of brain AD pathology) is elevated in depressed compared with non-depressed individuals consistently across studies, even in participants aged below 40 years [177]. Studies using cerebrospinal fluid markers of $A\beta_{42}$, arguably a more reliable measure of AD pathology, yield mixed results, showing lower, equal or greater levels in depressed versus non-depressed individuals [177]. The two existing neuroimaging studies of Aβ also report conflicting results [178, 179], and a study using a combined measure of Aβ and tau binding showed an association with depression and anxiety [180]. To our knowledge the one neuropathological study examining history of depression and AD pathology in non-clinical adults found no relationship [181]. Studies examining this relationship in individuals with clinical AD are also inconsistent, finding either no relationship [182], or a relationship with either neuritic plaques [183], neurofibrillary tangles [184] or both [185]. Additionally, these studies found either no interactive effect on clinical AD-risk or cognitive function [182] or that for a given level of function proximate to death, individuals with a history of depressive symptoms had greater pathology [183, 185].

Neuroticism was unrelated to AD pathology in two large longitudinal studies [45, 52, 186]; however controlling for the level of AD pathology, higher neuroticism was related to worse cognition and greater likelihood of dementia [46, 186]. Additionally in a separate longitudinal cohort study higher neuroticism was associated with greater neurofibrillary tangles and lower cognitive resilience to AD pathology (i.e., greater likelihood of developing symptomatic AD) [187].

Greater brain Aβ, measured by cerebrospinal fluid $A\beta_{42}$, has been associated with worse sleep quality [188]. This is supported by a neuroimaging study which showed that shorter sleep duration and worse sleep quality were associated with greater Aβ deposition [42]. Sleep is believed to involve lower synaptic activation in regions prone to Aβ aggregation, and greater clearance of Aβ via the glymphatic system [189], therefore these data support the findings that increased activity is related to increased Aβ aggregation. No studies have investigated the relationship between sleep and tau pathology. To our knowledge no investigations of the relationship between AD pathology and lifetime stress or PTSD have been conducted.

The relationship between AD pathology and Cognitive Debt remains unclear with as many studies finding a relationship between these factors as studies that do not. There is some indication that AD pathology is differentially associated with worse cognition when Cognitive Debt is present, but this relationship does not follow a systematic pattern, even when stratifying by disorder, pathology (Aβ or tau), or biomarker. These findings indicate that Cognitive Debt may exert its effects partially via traditional AD pathology, but also through a different mechanism.

ANNEX 2: Interventions

Pharmacologic interventions to reduce Cognitive Debt have produced mixed results. Anxiolytics and antipsychotics may increase risk of cognitive impairment, dementia, and mortality, therefore are not generally encouraged for use in older adults with memory impairment [190, 191]. Antidepressant medications increase hippocampal neurogenesis in animals and human cells [192, 193], likely acting through a common pathway that involves glucocorticoid receptors [194]. However the impact of antidepressants on cognition in older adults has been equivocal—the majority of studies report null or negative effects [195–197]. These seemingly contradictory findings may be explained by suboptimal dosing or the possibility that older adults with depression may have already entered the prodromal phase of AD, therefore would be unlikely to show improved cognitive function. In young adults, antidepressant treatment may attenuate rumination levels [198], thus may also reduce Cognitive Debt and AD risk. To our knowledge no studies have yet examined antidepressant use in early/midlife and late life cognitive impairment and dementia risk.

Turning to behavioural interventions, a recent systematic review concluded that cognitive behavioral

therapies (CBT) and mindfulness-based interventions reduce RNT [199]. Through the reduction of RNT, psychological distress and Cognitive Debt may also be minimized.

CBT emphasizes challenging negative thoughts and behaviors, and is amenable to transdiagnostic application [200]. Variants of CBT are effective in treating depression, anxiety, insomnia, and PTSD [201–204], however, trait neuroticism appears to mediate worse treatment efficacy [205]. Despite its promising results, when compared to pharmaceutical therapies or active control conditions, CBT does not seem to show greater efficacy. Watkins and colleagues adapted the standard CBT protocol to target rumination, the key maintaining process of depressive disorder. Their rumination-focused CBT differs from traditional CBT in that it focuses on changing the *process* of thinking rather than content of thought [206]. A phase II RCT reported greater treatment response and remission-rate, and lower relapse than the treatment as usual (medication) group [206]. Additionally, the changes in rumination appeared to mediate the relationship between treatment condition and depressive symptoms. While these findings are exciting, replication, particularly with active control groups, is necessary.

Mindfulness-based therapies promote non-judgmental awareness and attention to experiences of the present moment [207]. Individuals are encouraged to experience the flow of their thoughts with acceptance and without attempts to suppress or become preoccupied with them [208]. Mindfulness-based interventions have been used to alleviate symptoms of anxiety, depression, PTSD, and stress [209–211], and reductions in rumination and worry may mediate the impact of mindfulness on these symptoms [212]. Mindfulness-based interventions have been shown to exert an effect on the biological stress system, alter brain activation in the key regions implicated in Cognitive Debt, and also to improve cognitive function [213]. A recent review reported moderate effect sizes in clinical and non-clinical populations [214]. And there is suggestion that this approach may also be effective for PTSD [215] and sleep disorders [216]; however, again, these findings need replication.

The long-term impact of antidepressants, CBT and mindfulness-based therapies on cognitive decline and AD-risk has yet to be explored, and a consistent limitation of these studies is the lack of active control group and/or extended follow-up. Given these limitations there is cautious optimism that therapies exist, and may be effective in reducing Cognitive Debt.

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