Scientific Commentary on "**The development and convergence of co-pathologies in Alzheimer's disease"**

Co-pathologies and in Alzheimer's disease: Just multiple pathologies or partners in crime?

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Growing evidence suggests that dementia in the elderly results from multiple neuropathologies rather than from a strictly defined disease. Several pathologies have been found to co-occur in Alzheimer's Disease (AD) brains, which accumulate alongside τ tangles (NFTs) and amyloid β-protein (Aβ)-containing plaques, the two major neuropathological hallmarks of AD. Accordingly, pure AD is relatively rare. The topographical expansion of NFTs and amyloid plaques spreads in the human AD brain in a hierarchical, stereotypical manner (Braak and Braak, 1991; Thal *et al.*, 2002). Cerebral amyloid angiopathy (CAA), limbic-predominant, age-related TDP-43 encephalopathy neuropathological changes (LATE-NC) and Lewy body disease (LBD)-related pathology are well known to occur in AD brains as well (Montine *et al.*, 2012; Nelson *et al.*, 2019). The distribution of these pathologies and how they may interact with one another is, therefore, crucial for the development of the disease. In this issue of *Brain*, Robinson and colleagues examined the co-occurrence of CAA, LATE-NC and Lewy body pathology in demented and non-demented individuals (Robinson *et al.*, 2021). They further investigated the relationship of these pathologies with NFTs, amyloid plaques, age, and the apolipoprotein E (*APOE*) ε4 allele, i.e., the strongest genetic risk factor for AD.

To do so, Robinson *et al.* (2021) carried out a retrospective clinico-pathological study using two cohorts of 522 and 1340 participants. They conclude that in cases without dementia, increasing age was associated with all pathologies. In the presence of dementia, however, more advanced age was associated with LATE-NC, while younger ages associated with LBD pathology. The *APOE* ε4 allele was associated only with CAA in demented and non-demented cases. Additionally, both higher stages of the topographical expansion of NFTs, i.e, higher Braak NFT-stages (Braak and Braak, 1991), and of plaque pathology (Aβ phases in the medial temporal lobe) (Thal *et al.*, 2000) were associated with the topographical distribution of CAA – CAA stages (Thal *et al.*, 2003) - and LBD pathology (McKeith *et al.*, 2017). However, only Braak NFT-stages showed an association with LATE-NC distribution stages. Indeed, earlier studies already highlighted the relevance of combined age-related neuropathologies for the development of dementia (Attems and Jellinger, 2013; Kapasi *et al.*, 2017; Spires-Jones *et al.*, 2017; Robinson *et al.*, 2018). Specifically, the presence of infarcts or TDP-43 pathology in symptomatic AD

cases has been linked to more severe cognitive impairment (Snowdon *et al.*, 1997; Josephs *et al.*, 2016; Kapasi *et al.*, 2017; Hecht *et al.*, 2018). This suggests that underlying pathologies can contribute to the dementia risk and have a relevant interplay with AD.

In our own cohort of cases, we confirmed an age-related increase of the frequencies of NFTs, Aβ plaques, CAA, granulovacuolar degeneration (GVD), LATE-NC and Lewy bodies with an increase of the respective topographical expansion stage (Fig.1). In detail, we observed that with increasing age, higher Braak NFT stages and Aβ phases were found more frequently than in younger age groups (Fig. 1 a-b). The same was observed for CAA (Fig. 1 c). When we analyzed GVD pathology, a neuronal AD-associated lesion (Thal *et al.*, 2011), we also observed that higher stages are more prevalent with increasing ages (Fig. 1 d). Further, we have applied the LATE-NC stages to our cohort and we observed that TDP-43 pathology can already be detected in the age group of 41-60 years and that in the oldest old (81-98 years), TDP-43 pathology is most frequently extended to the frontal cortex (= LATE-NC stage 3) (Fig. 1 e). Finally, when using the Braak Lewy body disease (LBD) stages (Braak *et al.*, 2003), we observed that predominance of LBD is slightly more prevalent in individuals with 61-80 years old, compared to older individuals (81-98) (Fig. 1 f), which further supports the findings of Robinson *et al.* (2021) and Spires-Jones *et al.* (2017).

The main conclusion of Robinson *et al*. (2021) is that with increasing age the likelihood of developing multiple degenerative lesions in the brain increases and that there are additive effects of these pathologies to worsen the clinical degree of dementia. This is in line with previous studies on the occurrence of multiple pathologies in the brains of demented patients (Attems and Jellinger, 2013; Kapasi *et al.*, 2017; Spires-Jones *et al.*, 2017) and with similar additive effects on dementia in AD cases caused by additional cerebrovascular lesions (Snowdon *et al.*, 1997; Hecht *et al.*, 2018) and argyrophilic grain disease (Thal *et al.*, 2005). This has a significant impact on treatment regimes because targeting just Aβ and/or τ, which is the protein that accumulates in NFTs, may leave other drivers for dementia behind, i.e. α-synuclein in Lewy bodies, and TDP-43. Moreover, Aβ deposition in cerebral blood vessels (i.e. CAA) can cause blood flow alterations including infarcts (Mandybur, 1986; Hecht *et al.*, 2018) as well as bleedings (Mandybur, 1986) that lead to an additional damage of the brain parenchyma. Thus, a treatment regime targeting AD may need not only to reduce Aβ and τ but also reduce the progression of the other contributors to the development of dementia, i.e., LATE, LBD, GVD, and cerebrovascular lesions.

The general prevalence of LATE-NC, CAA, and GVD with more than 60% of the aged individuals above 80 years of age (Fig. 1) strongly argues in favor of an important role of these lesions for the development of AD, especially at higher ages. LBD is less frequent in our hospital-based cohort but still not negligible (approx. 40% of 60-80 years-old individuals). Moreover, the prevalence of these lesions and its cumulative effect towards the development of cognitive deficits to that of Aβ and τ may also raise the questions whether there are biological links between these pathologies. For CAA it is obvious. It is the same Aβ peptide that is deposited in plaques and in CAA. In transgenic mouse models with

neuronal overexpression of mutant amyloid precursor protein (APP), CAA is found in addition to plaques (Calhoun *et al.*, 1999). This means that we see neuronally-produced Aβ in CAA that is drained along the perivascular drainage channels and accumulates there as CAA. In capillaries, especially of *APOE* ε4 allele carriers Aβ deposition causes capillary CAA (Thal *et al.*, 2003) that leads to blood flow alterations in mouse models (Thal *et al.*, 2009) and is associated with allocortical microinfarcts in the CA1 region of the hippocampus (Hecht *et al.*, 2018). This chain of actions highlights the possible direct relationship between AD-related Aβ and vascular lesions as resulting from AD rather than from a typical cardiovascular/arteriosclerotic insult. Likewise, cross seeding and interaction of Aβ and α-synuclein has been described supporting interactions between AD and LBD (Ono *et al.*, 2012) as well as the synergistic effects described for α-synuclein and τ (Haggerty *et al.*, 2011). These finding support the presence of collaborative effects between Aβ and τ on the one hand, and Aβ and α-synuclein on the other. For GVD it was shown that τ-seeds can induce this pathology in cell culture (Wiersma *et al.*, 2019). This is in line with the correlation of the topographical spread of GVD with that of NFTs in AD (Thal *et al.*, 2011). Moreover, phosphorylated forms of τ, Aβ, and TDP-43 were reported in GVD (Köhler, 2016) further supporting links between GVD on the one hand and τ, Aβ, and TDP-43 pathology on the other. Moreover, TDP-43 cytoplasmic inclusions in AD sometimes reminisce the shape of NFTs and may colocalize with p-τ (Higashi *et al.*, 2007). Thus, in addition to the simple co-existence in the AD brain as observed neuropathologically, there is evidence that there are functional links/interactions between the "co-pathologies" that make them participating in the pathophysiology of AD. It is essential to take these interactions into account when targeting disease-related proteins. As obvious from the prevalence of these pathologies, except for LBD, these pathologies all become more prevalent with increasing age. For LBD there is a maximum prevalence between 60-80 years that decreases above 80 years. Whether this decrease is related to a lower general life expectancy of patients developing LBD-lesions needs to be further clarified.

Taken together, Robinson et al. (2021) indicate the relevance of all pathological contributors to the development of age-related dementia, which are seemingly "partners in crime, i.e. Aβ, NFTs, and the various co-pathologies. The presence of these pathologies and their spreading throughout the brain should not be overlooked when analyzing demented and non-demented brains. The co-pathologies should be considered as possible early therapeutic targets, as they are detected before the appearance of symptoms as well, i.e. in preclinical stages. Moreover, the overlap and co-accumulation of these pathologies with τ and Aβ pathology in demented cases highlights the importance of the interactions of these pathologies for the development of AD symptoms. Thus, diagnosis and therapy of dementia in the elderly should, therefore, include the multiple players in the disease to develop concepts for personalized treatment strategies for dementia.

Funding

The data included in Fig.1 were collected in projects funded by the Deutsche Forschungsgemeinschaft (TH624 4–1, 4–2, 6–1 (DRT); Germany), the Alzheimer Forschung Initiative (#10810, #13803 (DRT); Germany), Fonds Wetenschappelijk Onderzoek Vlaanderen (FWO G0F8516N, G065721N (DRT); Belgium) and Vlaamse Impulsfinanciering voor Netwerken voor Dementieonderzoek (IWT 135043 (DRT); Belgium).

Competing Interests

DRT received speaker honorarium from Novartis Pharma Basel (Switzerland) and Biogen (USA), travel reimbursement from GE-Healthcare (UK), and UCB (Belgium), and collaborated with GE-Healthcare (UK), Novartis Pharma Basel (Switzerland), Probiodrug (Germany), and Janssen Pharmaceutical Companies (Belgium).

Figure legend

Figure 1 – Pathological proteins accumulate with increasing age in a hospital-based cohort. Age-related prevalence of stages of NFT pathology (Braak NFT stages) (Braak and Braak, 1991) (**a,** n = 1325), Aβ plaque pathology (amyloid phases) (Thal *et al.*, 2002) (**b**, n = 136), CAA (CAA stages (Thal *et al.*, 2003)) (**c**, n = 284), granulovacuolar degeneration (GVD stages) (Thal *et al.*, 2011) (**d**, n = 227), LATE-NC (LATE-NC stages) (Nelson *et al.*, 2019) (**e**, n = 97) and Lewy body pathology (Braak LBD stages) (Braak *et al.*, 2003) (**f**, n = 583). Some cases included here were previously analyzed in a similar manner for some of these pathologies (Spires-Jones *et al.*, 2017).

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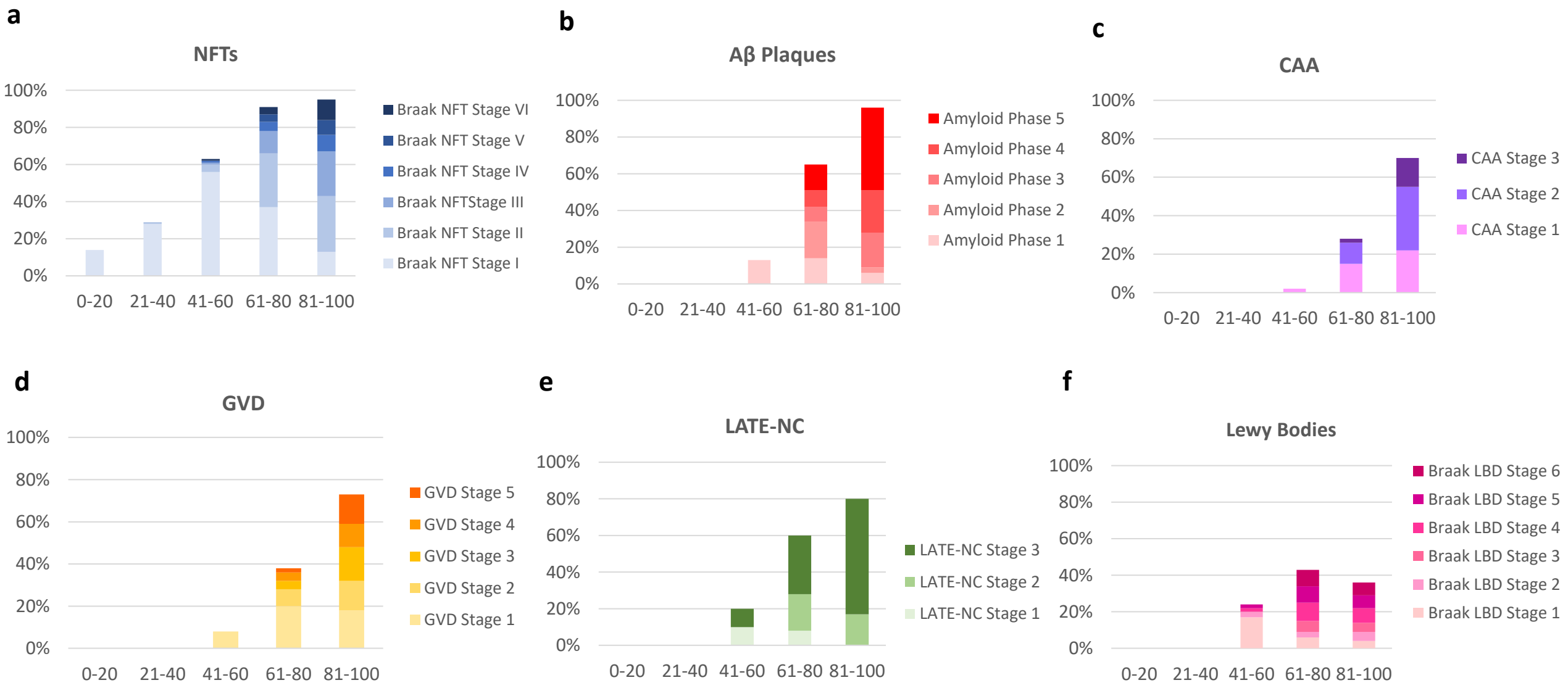
a
NFTs
100%
80%
60%
40%
20%
0%
0-20
21-40
41-60
61-80
81-100
Braak NFT Stage VI
Braak NFT Stage V
Braak NFT Stage IV
Braak NFTStage III
Braak NFT Stage II
Braak NFT Stage I
b
Aβ Plaques
Amyloid Phase 5
Amyloid Phase 4
Amyloid Phase 3
Amyloid Phase 2
Amyloid Phase 1
c
CAA
CAA Stage 3
CAA Stage 2
CAA Stage 1
d
GVD
GVD Stage 5
GVD Stage 4
GVD Stage 3
GVD Stage 2
GVD Stage 1
e
LATE-NC
LATE-NC Stage 3
LATE-NC Stage 2
LATE-NC Stage 1
f
Lewy Bodies
Braak LBD Stage 6
Braak LBD Stage 5
Braak LBD Stage 4
Braak LBD Stage 3
Braak LBD Stage 2
Braak LBD Stage 1