Amygdalar subnuclei are particularly affected in *MAPT*/FTDP-17, Pick's disease and TDP-43 type C-associated frontotemporal dementia

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Background

Frontotemporal dementia (FTD) is a heterogeneous neurodegenerative disorder, with frontal and temporal atrophy. Subcortical involvement has been described too, but no study has so far focused on the amygdalar subnuclei (AS). The amygdala is composed of different subnuclei with mainly connections to the limbic system. It is involved in different aspects of reward learning, motivation, emotion, and in several cognitive functions (Figure 1).
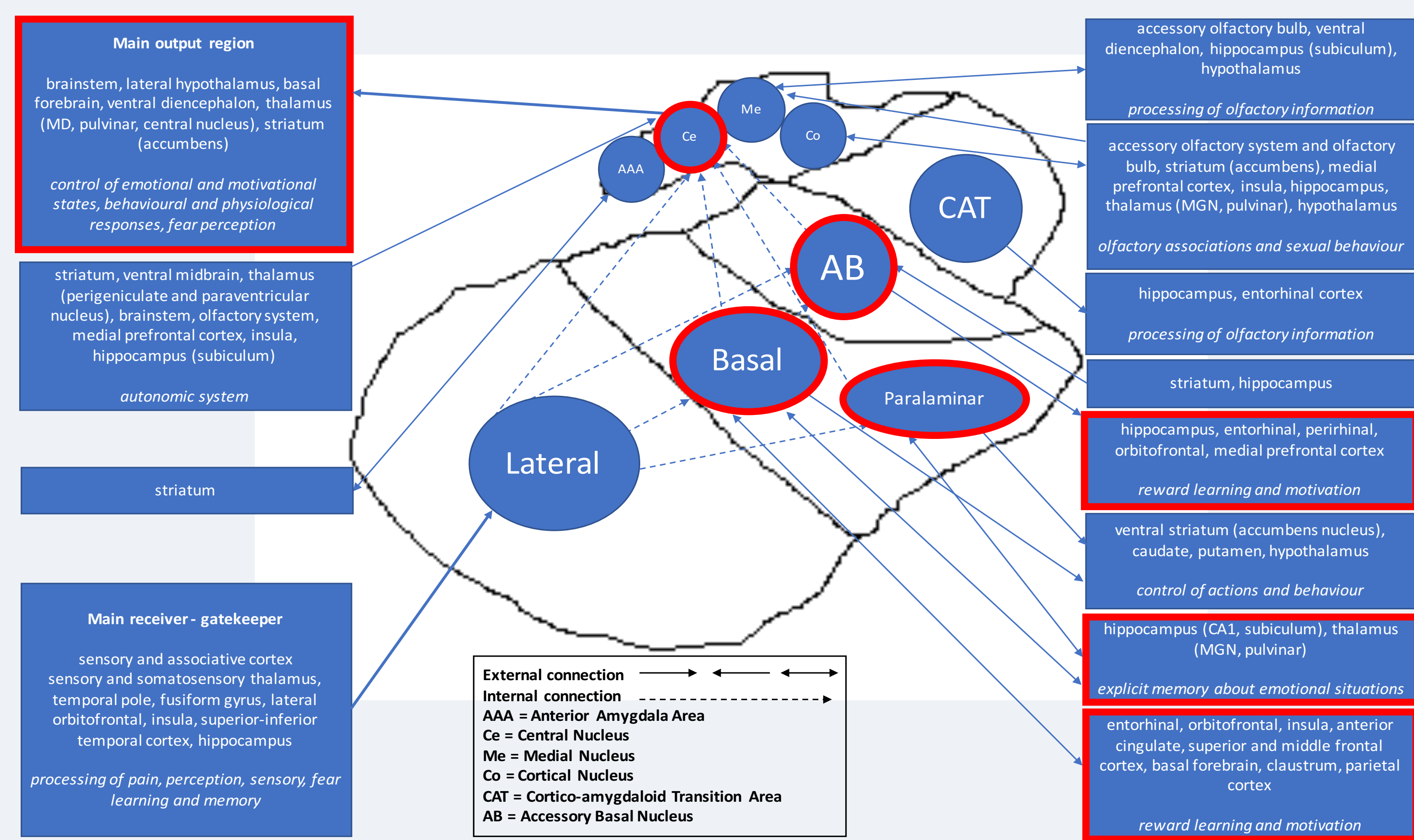

Figure 1. Schematic representation of the AS, their functions and connections. Red-bordered boxes and subnuclei are part of the limbic system.

Methods

We investigated AS involvement in a cohort of 132 patients with a genetic or pathologically confirmed diagnosis of FTD (age: mean (standard deviation) 61(8) years; disease duration: 5(3) years) compared with 107 age-matched controls (age: 63(11) years). We assessed subgroups stratified by genetic diagnosis (27 *MAPT*, 29 *C9orf72*, 18 *GRN*) and pathological confirmation: FUS (n=3), TDP-43 type A (n=16), TDP-43 type B (n=3), TDP-43 type C (n=20); tau with Pick's disease (n=17), with PSP (n=4), with CBD (n=9), and due to FTDP-17 (n=7).

We performed an automated segmentation of T1-weighted MRIs to extract AS volumes (lateral, basal/paralaminar, accessory basal, superficial nuclei, cortico-amygdaloid transition area), using a customised version of the module available in FreeSurfer 6.0 [Saygin *et al.*, 2017], to adapt the output of GIF (geodesic information flow (GIF) algorithm [Cardoso *et al.*, 2015]) to the FreeSurfer format.

Based on the volumes of the left and right hemispheres, we defined the most severely affected cerebral hemisphere in each patient, and we analyzed the AS volumes accordingly. We performed a linear regression analysis adjusted for age, gender, total intracranial volume, and scanner type.

We also investigated asymmetry by calculating an Asymmetry Index, defined as the absolute difference between the left and right total amygdalar volumes in relation to the total bilateral volume: l(Left - Right)l/(Left + Right).

Results

Overall, FTD patients had smaller AS than controls (29-34% difference for the most affected hemisphere, 23-26% for the least affected, p<0.0005).

MAPT group had the smallest AS in both hemispheres (37-43%, p<0.0005), while *C9orf72* and *GRN* showed the most involvement in the superficial group and accessory basal subnucleus (24-29%, p<0.0005).

Stratifying by pathology, FTDP-17, TDP-43 type C and Pick's disease were the most impaired groups, especially for the superficial (39-47%), accessory basal (38-50%), and basal/paralaminar subnuclei (35-39%, p<0.0005) in the most affected hemisphere (Figure 2). FUS showed a very homogenous involvement across all AS (28-31% for the most affected, 26-28% for the least affected hemisphere, p<0.003).

For most groups, no differences were seen between the right and left amygdalae, except for the *GRN*, Pick's disease, CBD, and TDP-43 type C groups which had an asymmetry index significantly greater than controls (p<0.003).
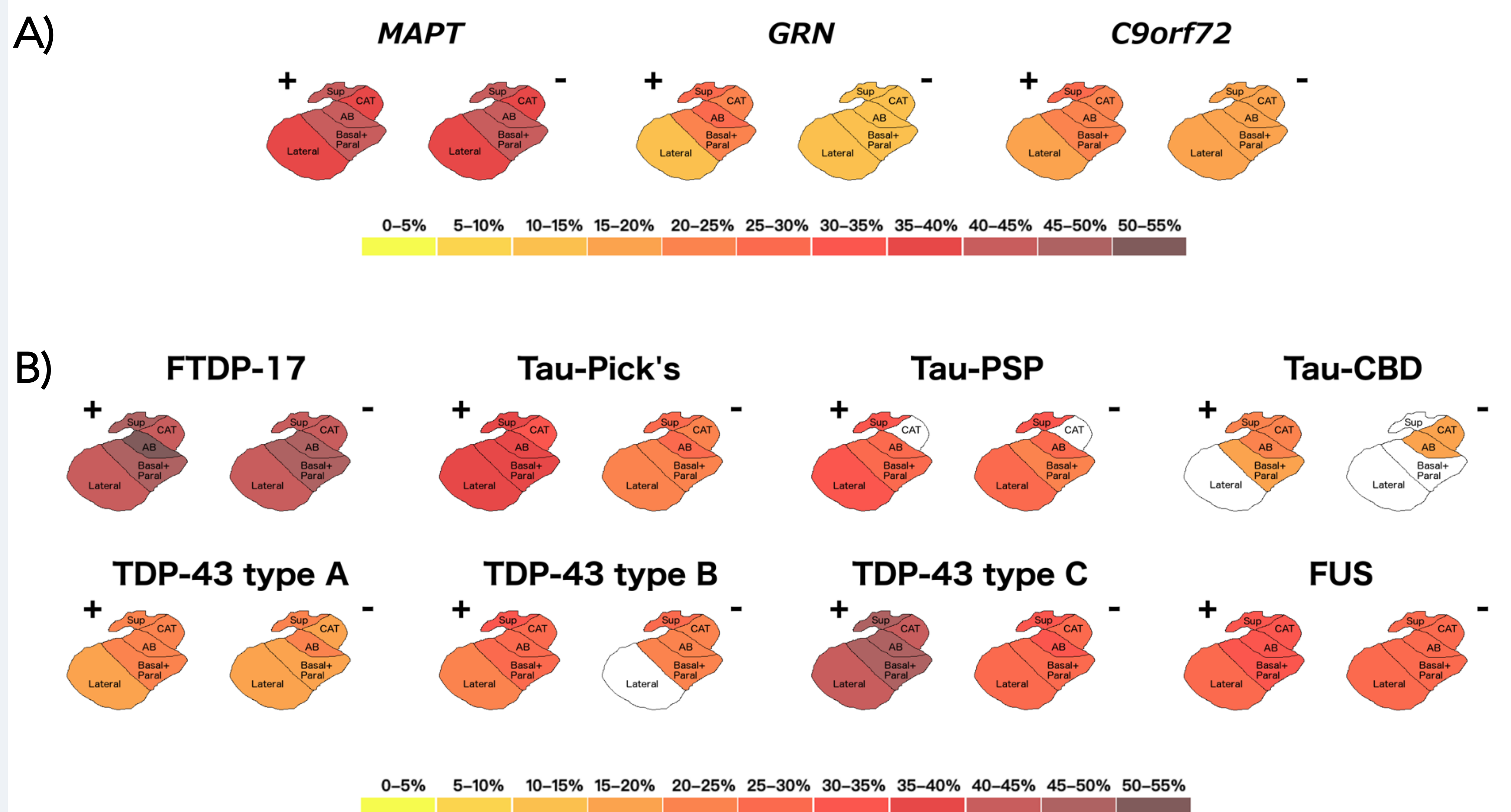

Figure 2. Pattern of atrophy in the AS in the genetically A) and pathologically B) confirmed FTD cases. Colour bar denotes the % difference in volume from controls. + denotes the most affected and - denotes the least affected hemisphere.

Conclusions

The AS were most affected in *MAPT*/FTDP-17, Pick's disease and TDP-43 type C. The most affected subnuclei were the superficial group, accessory basal, and basal/paralaminar which are part of the reward system and involved in emotion regulation.