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Research article

Accelerated Cognitive Ageing in epilepsy: exploring the effective connectivity between resting-state networks and its relation to cognitive decline

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ABSTRACT

Objective: This study aims at understanding the dynamic functional brain organization in Accelerated Cognitive Ageing (ACA) in epilepsy. We also assess to which extend the (abnormal) effective connectivity between brain networks correlates with the (estimated) decline in IQ scores observed in the ACA patients.

Material and methods: Two multi-echo resting-state fMRI scans of 10 ACA patients and 14 age- and education-matched healthy controls were acquired. A task-based fMRI was acquired in-between those two scans, for possible cognitive fatigue effects on reserve capacity. Granger causality (GC), a measure of effective connectivity between brain regions, was applied on 7 major cognitive networks, and group-wise compared, using permutation testing statistics. This was performed on each of the resting-state sessions independently. We assessed the correlation between the cognitive deterioration scores (representing cognitive decline), and the paired-networks granger causality values.

Results: The cingulate cortex appeared to be more engaged in ACA patients. Its dynamics towards the right fronto-parietal cortex, salience network, and the dorsal attention networks (DAN) was stronger than in controls, only in the first resting-state scan session. The Granger causality from the DAN to the default mode network (DMN) and from the ventral attention network (VAN) to the left fronto-parietal network (FPL) was also stronger in ACA patients and again only in the first scans. In the second resting-state scans, only the DMN was more strongly connected with the cingulate cortex in ACA patients. A weaker GC from DMN to FPL, and stronger GC from the salience network to cingulate cortex were associated with more decline in the Full-scale IQ and more GC from DMN to VAN would lead to more decline in the Perceptual Reasoning Index in ACA.

Conclusion: The results are in line with the hypothesis of over-recruitment at low cognitive load, and exhaustion at higher cognitive load, as shown by the compensation-related utilization of neural circuits hypothesis (CRUNCH) model for ageing. Moreover, the DMN to VAN directed connectivity strongly correlates with the (estimated) decline in the Perceptual Reasoning Index, which is also in line with a recent study on ageing with mild cognitive impairment in elderly, and the posterior-anterior shift in aging (PASA) model. This study therefore supports the idea that the cognitive decline in our patients resembles the decline observed in healthy ageing, but in an accelerated mode. This study also sheds light on the directions of the impaired connectivity between the main networks involved in the deterioration process, which can be helpful for future development of treatment solutions.

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1. Introduction

Cognitive impairment is a common comorbidity in patients with epilepsy. It has been estimated that up to 65% of all patients with epilepsy show cognitive impairment, which also account for about half the burden of disease [1, 2]. Such impairments have frequently been reported in literature but only for specific cognitive functions, for specific types of epilepsy, e.g., memory impairments in temporal lobe epilepsy, or executive function impairment in frontal lobe epilepsy. Cognitive decline (i.e. global cognitive deterioration) is less frequently reported [3, 4, 5, 6]. In addition, more global cognitive decline had been already identified with the induction of the concept of epilepsy dementia by Growers in 1889 [7]. Research on this epilepsy comorbidity suggests that it almost exclusively occurs in case of child on-set epilepsy where accumulation of medication and (tonic-clonic) seizures over decades yield to gradual decline of higher cognitive functions. Therefore, the decline is viewed as a 'chronic accumulation' model, where the cognitive outcomes of the patients resembles those in dementia. However, recently we proposed a new 'cascadic' model of cognitive decline in epilepsy [4], where patients display cognitive deterioration but do not meet the criteria of Alzheimer Disease or the aforementioned epilepsy dementia comorbidity. The process is seen in adult-onset epilepsy and seem to mimic 'healthy' brain ageing, but at a higher speed. Hence this cognitive decline has been termed Accelerated Cognitive Ageing (ACA) [4]. As the patients in this subgroup often suffer other brain pathology before the onset of epilepsy, the decline is 'cascadic' and represents a double hit phenomenon: where the first 'hit' makes the brain vulnerable but still recovers due to cognitive reserve capacity, and the second 'hit' irreversibly damages the brain and its cognitive capacity, and leads to ACA [8]. More specifically a clear global cognitive deterioration takes place in relatively short period of time after the (usually late) onset of epilepsy (the second hit) on individuals with an already reduced reserve capacity from a traumatic brain injury, or (cardio)vascular diseases (the first hit).

The neurological mechanism of action of ACA is poorly understood. Functional MRI studies can shed light on such mechanisms and can give information on which brain areas or networks are involved, by comparing functional networks in ACA patients to a control group. In our previous work we showed that Granger causality can be used in neuroimaging to assess causality between time series of the fMRI signals (dynamic functional connectivity) [9]. Indeed, in several neuropsychiatric disorders, such as ADHD, autism or depression, effective dynamics appeared to be a powerful tool in describing neuronal correlates of such pathology [9, 10, 11]. In the present study, we use the same technique, i.e. dynamic functional connectivity (Granger causality) in an attempt to find relevant mechanisms of action of the ACA epileptic co-morbidity, more specifically in the dynamics between cognitive-related functional brain networks.

2. Methods

2.1. Participants and cognitive measures

Fourteen adult outpatients with a confirmed diagnosis of epilepsy and ACA were recruited from the centre for epilepsy Kempenhaeghe (Heeze, the Netherlands). For a description of the diagnostic process and the clinical characteristics of the included patients see [12]. The ACA patients were consecutively age- and education-matched with 16 healthy controls with no history of neurological or psychiatric illness. This study was approved by the Local Medical Ethical Committee. All subjects signed informed consent. 70% of ACA patients had at least one co-morbidity, in which 57% were cerebrovascular, and 43% cardiovascular co-morbidities.

After checking and pre-processing the fMRI-data, four ACA-patients and two healthy controls were excluded due to excessive head motion (n = 3), MRI artefacts (n = 2) and an unexpected detection of a brain tumour (n = 1). The effective sample therefore consisted of 10 ACA-patients and 14 healthy controls. Main demographic and clinical data are shown in Table 1. Importantly, deterioration scores were calculated by subtracting the estimated premorbid IQs (OPIE-IV scores [13]) from the actual IQs, resulting in three IQ-deterioration scores: det-FSIQ, det-VCI and det-PRI.

2.2. MRI protocol

T1-weighted anatomical images were acquired using a 3.0 T imaging system (Philips Achieva) with a 3D Fast Field Echo (FFE) sequence: echo-time (TE) = 3.8 ms; repetition time (TR) = 8.4 ms; inversion time (TI) = 1035 ms; flip angle (FA) = 8 deg.; field of view (FOV) = 240 × 240 mm^2, with 180 sagittal slices; voxel size = 1 × 1 × 1 mm^3; and SENSE factor = 1.5.

All subjects underwent a series of functional MRI sessions: two resting-state (RS) fMRI scans and one task-based scan with an activation paradigm in between (silent word-generation task). The first resting-state fMRI scan (RS1) provided the baseline functional architecture in both subject groups. The following task-based fMRI-scan served as a means of initiating cognitive (task-based) activity. Data of this scan were not further analyzed. The second resting-state scan (RS2) revealed whether functional connectivity changed after cognitive effort. FMRI data were acquired using multi-echo echo-planar imaging (ME-EPI) sequences with 3 echoes: TEs = 12, 35, 58 ms, TR = 2 s; FA = 90 deg.; SENSE factor = 2.7; 208 dynamics for a total scan time of 7 min; 27 axial slices (with no gap), 64 × 64 matrix FOV, with a 3.5 × 3.5 × 4.5 mm^3 voxel size. Figure 1 shows the MRI protocol the participants underwent. In this study only RS1 and RS2 are analyzed, compared between the groups, and correlated with ACA psychological deterioration scores, as explain in the next sessions.

2.3. Preprocessing and resting-state network extraction

First, data were preprocessed to be denoised and normalized. We used the pipeline of Kundu et al., to clean all fMRI data of each individual and each session [14]. Briefly, these steps were co-registration to the T1-weighted anatomical images, followed by a co-registration of MNI152 space. Also slice timing correction, and head-motion correction was applied. The benefit of using multi-echo being that one can model the T2* decay. Using this T2* maps, a weighting on each voxel and for each echo is done and the echoes are then optimally combined. This maximizes the BOLD SNR. However, noise is still present in these normalized fMRI data, and non-BOLD signal remains. Hence the multi-echo (ME) Independent Component Analysis (ICA) cleaning is performed [15]. Independent components are ranked through a goodness-of-fit method, to be split into BOLD and Non-BOLD components. After regression of the bad components upon the optimally combined-echo fMRI scans, multi-echo cleaned resting-state fMRI data are obtained for each participant/session [16]. This ME-ICA cleaning has been proven to be the most robust de-noising methods for resting-state fMRI, and to improve substantially statistical power [17, 18].

Second, in order to extract resting-state networks (RSNs), we temporally concatenated all the aforementioned ME-ICA cleaned scans (all participants and sessions), and applied the group-ICA method [19] implemented in FSL (https://fsl.fmrib.ox.ac.uk/fsl). The multi-echo cleaning preprocessing, described in the previous paragraph, found in average (among all participant/scans) 18 activity-related independent component (or networks). Therefore, we chose 18 degrees-of-freedom for our group-ICA decomposition, to extract 18 group-RSNs. After the group-ICA, dual-regression is used to obtain the subject-specifics components (RSNs) and their time series associated [20]. After matching our RSNs maps with Smith and colleagues' brain template of the 10 most relevant resting-state networks, and after visual inspection, we selected 14 effective networks and 4 artefactual ones (see Figure 2A) [21,22].

Table 1. Demographic, clinical, and psychological characteristics of included subjects.

	ACA	Healthy controls
Age in years M (SD) range	61.3 (8.9) 50-74 y	62.2 (9.8) 47-79 y
Gender	70.0% male	35.7% male
Handedness	100.0 % right-handed	92.9% right-handed
Age at epilepsy onset M (SD) + range	35.0 (14.6) 15-59 y	-
Duration of epilepsy M (SD) + range	22.3 (15.2) 1-50 y	-
Type of epilepsy	40.0% cryptogenic localization-related 40.0% symptomatic 20.0% idiopathic	-
Dominant seizure type[a]	10.0% simple partial 20.0% complex partial 20.0% absence 0.0% tonic-clonic 50.0% seizure free	-
Status epilepticus	50.0% yes	
Seizure frequency	50.0% seizure (sz) free 0.0% < 1 sz/y 20.0% 1–5 sz/y 20.0% 1 sz per 2 months 0.0% monthly sz 10.0% weekly sz 0.0% daily sz	-
Drug load[b]	1.5 (0.4)	-
WAIS-IV indexes FSIQ VCI PRI WMI PSI	76.7 (8.7)* 94.7 (10.6) 75.8 (6.9)* 79.6 (10.0)* 67.0 (14.4)*	108.4 (13.4) 106.2 (12.2) 103.2 (13.8) 104.9 (13.3) 114.6 (8.7)
Deterioration scores[c] Det-FSIQ Det-VCI Det-PRI	-22.1 (5.0)* -0.5 (8.9) -21.0 (4.5)*	-1.3 (8.2) 0.2 (6.0) 0.0 (8.7)
Memory scores Auditory Visual Delayed memory	93.9 (9.7)* 92.7 (7.0) 93.5 (8.4)*	109.9 (12.6) 102.8 (10.9) 106.3 (10.9)

Note: * = p < 0.01 sign. difference between groups. WMI: Working Memory Index. PSI: Processing Speed Index.

[a] Dominant seizure type is determined for the two years preceding neuropsychological assessment.

[b] The prescribed daily dose of antiepileptic medication divided by the defined daily dose.

[c] Deterioration scores = [WAIS-IV (actual) IQ-scores - OPIE-IV (pre-morbid) IQ-scores].

2.4. Granger causality and statistical analyses

The selected RSNs have a time-series associated. These time courses are used to apply Granger causality (GC) for all pairs of RSNs under consideration. One signal Y is said to Granger cause another signal X, if the past of Y and X can better predict the future of X rather than with the past of X only [23]. The estimation of the F-statistics of GC strength, that describes directed functional connectivity, i.e. causality, between two networks time-series, were extracted using the MVGC toolbox [24]. This was applied on all participants' scan sessions. The terms 'causal', 'directed', 'dynamic', or 'effective' (functional) connectivity, represent the same concept of pairwise (between-network) GC, and are here interchangeable.

After obtaining each participants' GC adjacency matrix, where each entry represents a directed pairwise causal connection, a group comparison can be conducted. Since F values from GC were not normally distributed, we applied an exact (permutation) statistical testing, in order to find differences between ACA and Controls in their brain network causality. For all participants and the RSNs we applied 5000 permutations followed by 2-samples 1-sided t-tests. If our 'true' (ACA vs CON) T-score is greater than the 97.5 percentile of all the other T-scores, we can affirm significances in the difference between the cohorts (similar to having an alpha = 0.025 in a parametric 2 sample 1-sided t-tests). This was repeated for both sides, to see when ACA > CON and when CON > ACA in the between-networks causality strengths; and for the two resting-state scans (RS1 and RS2), to see differences or similarities between the two sessions, and get insights on the effect of the task-based fMRI that was acquired in-between.

Finally, we also correlated the psychological deterioration (det-) scores with the aforementioned GCs for all ACA participants. Deterioration scores are negatively signed, hence a positive correlation between det-scores and GC values would mean that with higher causality between two networks, the less deterioration is observed. Conversely, the more causality, the more deterioration, would be shown by a negative correlation. This correlation analysis was also performed on a setup wherein IC time-series from RS1 and RS2 were normalized and concatenated before undergoing the GC analysis described above. If effective connectivity of a pair of RSNs correlates with a deterioration score in all of the 3 setups (RS1, RS2, and RS1/RS2 concatenated), we have strong evidence that the pairwise directed connectivity is associated with the accelerated cognitive decline, no matter the resting states the participants are experiencing (pre-task RS1, or post-task RS2). Hence, consistent results of significant correlations ensure reproducibility and independency of the results to the cognitive load or brain exhaustion state, making them strong predictors, or biomarkers of the ACA phenomenon.

3. Results

3.1. Resting-state networks selection

Using the group-ICA decomposition of FSL, we extracted 14 effective subject-specific spatial maps (RSNs) and their associated time series. Out of these 14 networks, 7 were relevant for our study. We retained the cognitive-related networks and removed sensory motor cortices and visual system networks. Furthermore, cerebellar networks were excluded. The 7 aforementioned networks used in our study are presented in Figure 2, and are comprised of the Default-mode network (DMN), the fronto-parietal right and left (FPR, FPL) networks, the Cingulate cortex network (CING), the Ventral and Dorsal Attention Networks (VAN, DAN) and the Salience Network (SN).

3.2. Granger causality differences

Using the 7 relevant networks we applied Granger causality for all (42) pairs of networks and compared the strength of the effective connectivity between the groups. Figure 3 shows the results of the statistical comparison, for each resting-state scan separately.

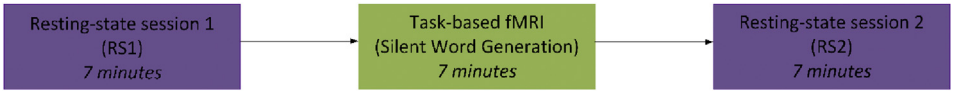

Figure 1. MRI protocol.

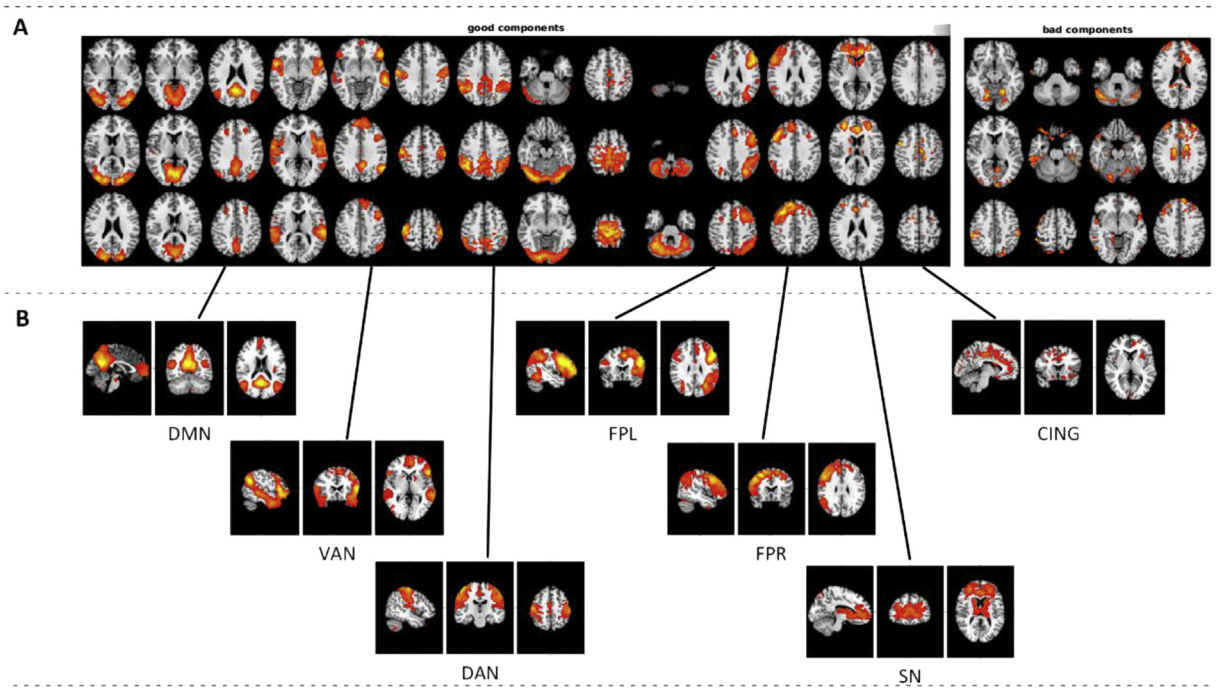

Figure 2. A) Networks extracted from group-ICA, the 'good' networks on the left, and the 'bad' networks (noise) on the right; B) Cognitive-related networks wherein their time series (network fluctuations) are used for the Granger (dynamics) analysis.

In RS1, the ACA group displayed a stronger causal connectivity as compared to controls. For 3 directed effective connections from the cingulate cortex: CING - > FPR, and CING - > SN, CING - > DAN; for an effective connectivity from the ventral attention network: VAN - > FPL; and for the pair DAN - > DMN. Also, in RS1, the ACA group showed a weaker dynamic connectivity for the directed connectivity DAN - > FPR.

Regarding the second resting-state session ACA were significantly stronger in their effective connectivity only for the pair: DMN - > CING. We summarized our strongest (lowest p-values) evidence of group difference results in pairwise granger causalities, involving the cingulate cortex, in Figure 5A.

3.3. Correlation between Granger causality and deterioration scores (in ACA)

In a post-hoc analysis we calculated the (Pearson) correlations between the Granger causality values between pairs of networks, and their deterioration scores. Figure 4 depicts the statistically significant results (correlation p-value < 0.05), per resting-state session. This was only performed for the ACA patients as deterioration scores in the controls were approximately 0. The effective connectivity FPR - > SN, and SN - > CING correlated negatively with the deterioration in full scale IQ in RS1, whereas in RS2, DMN < - > FPL (both directions), DAN - > SN negatively

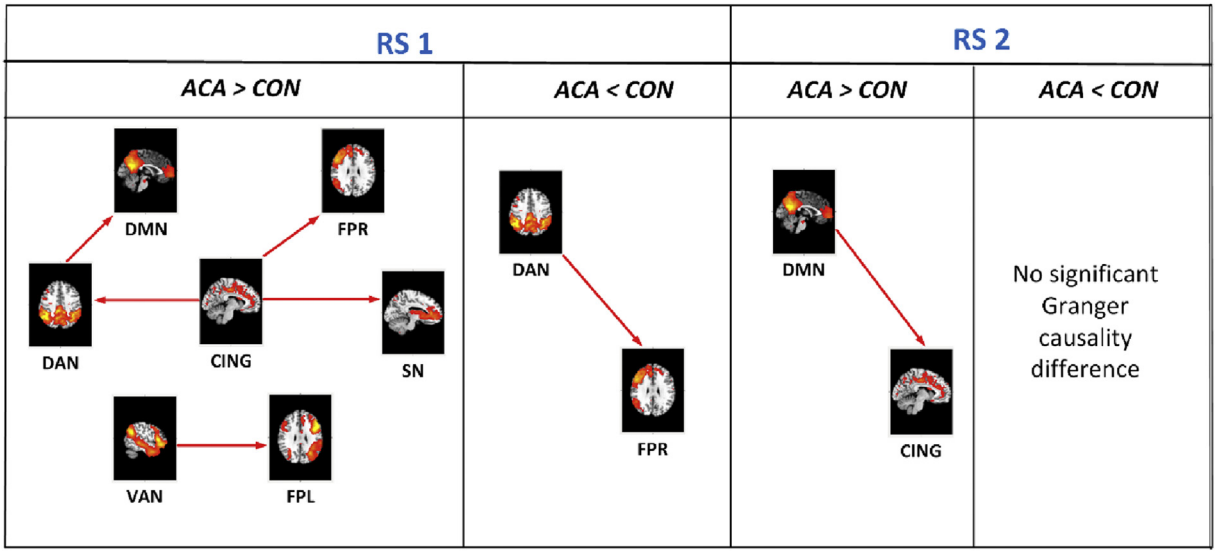

Figure 3. Pairs of networks that showed differences in causality strength between patients and controls, in resting-state session 1 and 2. Red arrows indicate the direction of the causal connectivity between networks.

correlates and SN - > VAN positively correlates with det-FSIQ. For the RS1/RS2 concatenated time-series analysis, det-FSIQ positively correlates with the dynamics DMN - > FPL, and negatively correlates with Granger causality SN - > CING.

Regarding correlation with det-PRI scores, in the 3 setups (RS1, RS2, RS1/RS2 concatenated) patients had a negative correlation with the effective connectivity DMN - > VAN. The dynamics FPL - > SN showed positive correlation with deterioration scores, i.e., less FPL - > SN causal connectivity would lead to greater deterioration.

The Granger causality from DMN to VAN was consistently associated with det-PRI in ACA patients, i.e. the effect was present in RS1, RS2, and the RS1/RS2 concatenation set-ups. This consistency was not found for det-FSIQ. Also, the decline in PRI is the most relevant psychological characteristics for diagnosing ACA. Therefore, the correlation between DMN- > VAN GC and the det-PRI score is our main and most reliable significant result and is depicted in Figure 5B.

4. Discussion

Many fMRI studies have identified age-related changes in within-network functional connectivity but few have reported an association of between-network connectivity and age-related cognitive deficits [25, 26]. Researchers have mainly focused on DMN connectivity, using correlation methods [27]. Also, decreased connectivity within the nodes of the main RSNs, including the DMN, salience, executive, and attention networks has been shown. These results has been observed using ICA [28, 29], seed-based connectivity [30], and graph-theory in a whole brain approaches [31, 32]. Similar research has been done in case of mild-cognitive impairment in elderly [33]. Few studies have investigated the effective connectivity within cognitive networks. In these studies, the effective connectivity within and between the DMN, dorsal attention networks and salience networks were studied in ageing [34, 35]. In our study, we conducted an effective connectivity analysis (Granger causality), not only for the DMN, DAN, and SN, but also the FPL, FPR, CING, and VAN (i.e., the executive-control networks). It is shown that the latter networks are the pillars of cognitive processing, and take part of the DMN, SN, and EXE triad useful for rest-task switching [29, 36, 37], and task flexibility [38]. This task switching and flexibility is an important impairment in ACA patients [8, 12].

Our results suggest that ACA patients have stronger between-networks effective connectivity from the cingulate cortex compared to the age- and education-matched control participants. We showed that CING over-recruits the fronto-parietal (executive) networks (FPR, SN, DAN) in the baseline resting state fMRI (main group-difference results in Figure 5A). This is in line with the *compensation-related utilization of neural circuit hypothesis* (CRUNCH) model that has been proposed to describe the use of compensatory mechanisms in ageing [39]. Briefly, CRUNCH proposes that older adults recruit greater neural resources to compensate at a lower cognitive load but that at a higher cognitive load, older adults show equivalent or lower activation and worse cognitive performance compared with young adults [26, 40]. This effect has been observed in the PFC and also in the parietal cortex, concretely in the precuneus and posterior cingulate and both in episodic memory tasks and in working memory tasks [25]. Our DAN, FPR, and SN are clearly the constituent networks of the PFC and parietal cortex and are more strongly causally connected from the CING in RS1 as compared with controls. Hence, we may hypothesize that ACA patients recruit greater neural resources to compensate as seen at the baseline rest (RS1, low cognitive load). However, after cognitive activation (task-based fMRI), such compensatory mechanisms fail and in the second resting state scan (after a cognitive task) ACA patients showed equivalent or lower activation as compared with healthy elderly. The over-recruitment of CING

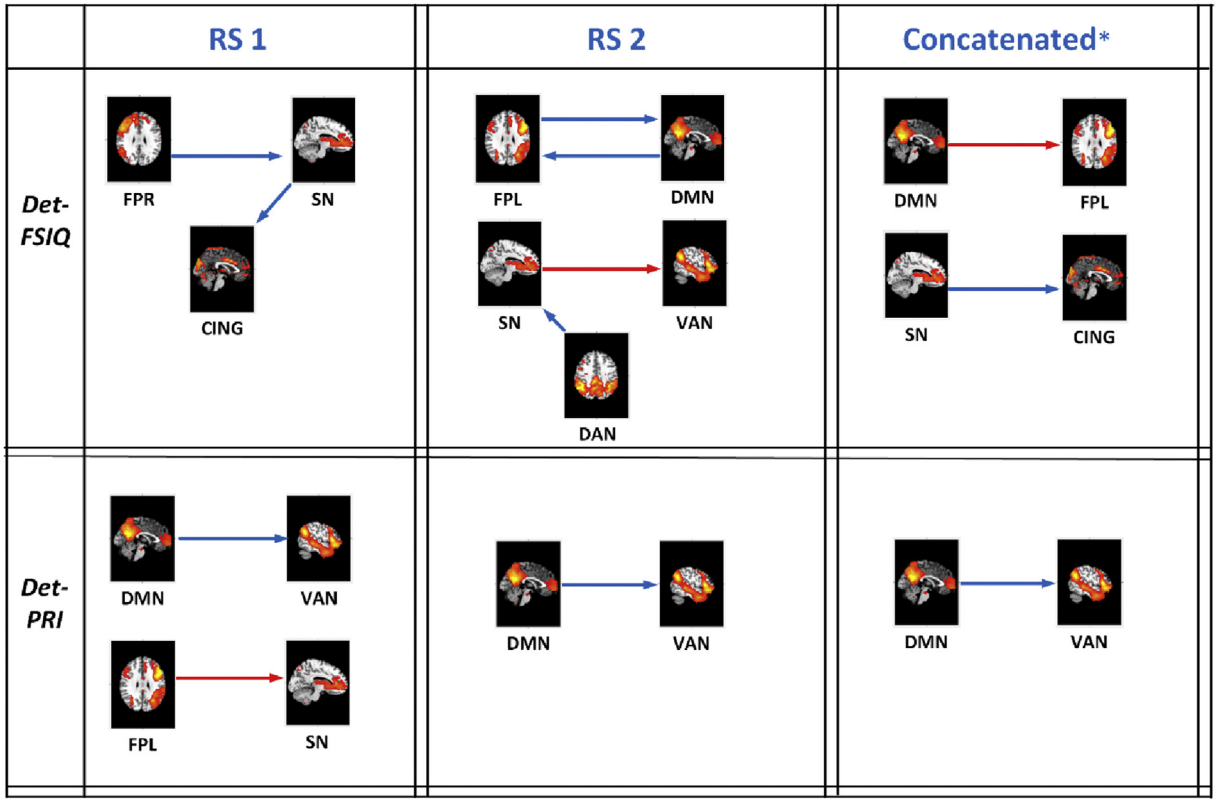

Figure 4. Significant correlation between effective connectivity (Granger causality) and the psychological deterioration scores; negative correlation (anti-correlation) in blue arrows; positive correlation in red arrows. Note: a negative correlation means that the more negative a deterioration score is, i.e. higher decline, the stronger the effective connectivity is. Whereas for a positive correlation: the higher the decline is, the lower the effective connectivity strength is. *RSN time series from RS1 and RS2 of each participant were normalized and concatenated before undergoing the GC analyses.

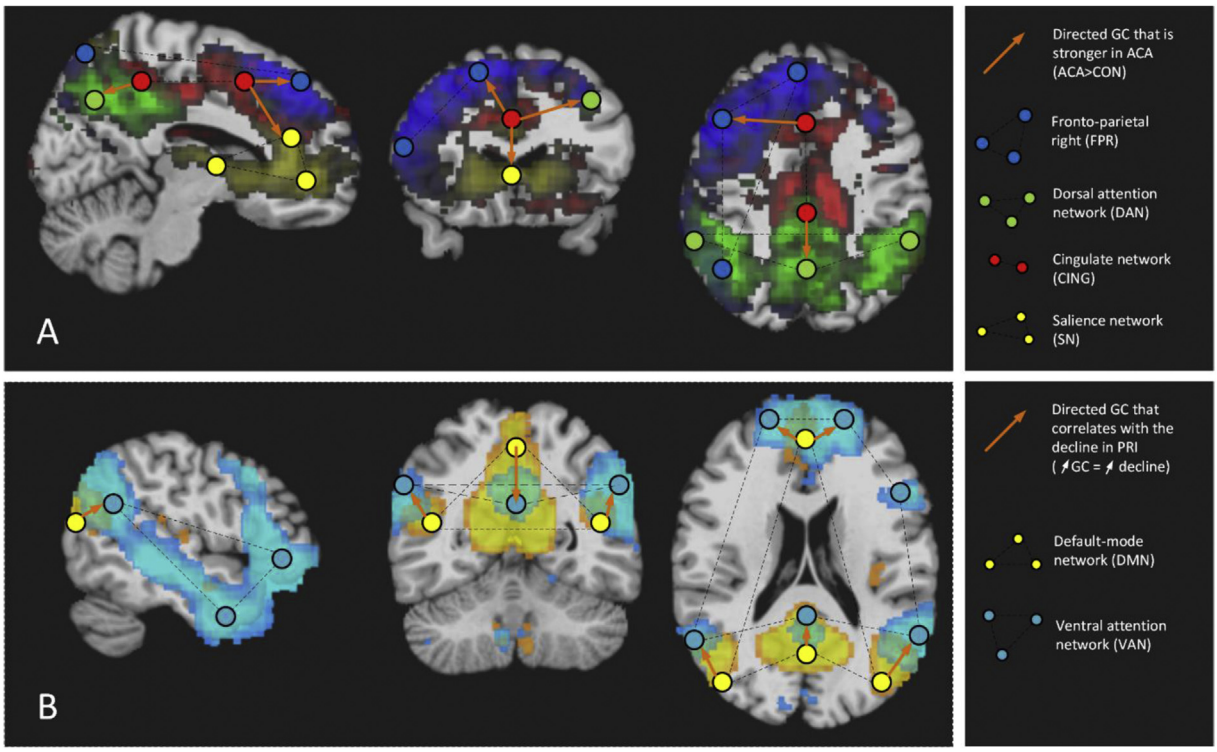

Figure 5. (A) Main evidence of abnormal connectivity in ACA, with increased GC between the cingulate cortex and three cognition-related RSNs; (B) and the most consistent (in RS1 and RS2) correlation between the GC and the decline in Perceptual Reasoning Index (det-PRI) in ACA.

towards the other cognitive networks is also supported by the study of Cao et al. where ageing has proven to have an effect on the resting-state functional connectivity in anterior cingulate cortex, with increased connection with salience network parts (CING - > SN) but reduced integration with DMN [41]. Also, the increased dynamic connectivity from CING and the decreased connectivity DAN - > FPR in ACA can be explained by the *Posterior-Anterior Shift with Aging* (PASA) model [42]. PASA hypothesizes deficits in ageing to activate regions in the posterior midline cortex — as for our reduced DAN - > FPR — accompanied with increased activity in medial frontal cortex — as for our CING-related dynamics. In this regard, this posterior-anterior shift commonly results in the disconnection between the anterior and the posterior nodes of the DMN, which correlates with age-related cognitive decline [28, 30]. More research has shown evidence that ageing reduces within-DMN connectivity and increases connectivity between the DMN and external regions [25]. The within-network decrease and between-network increase of connectivity can be seen as a decreased network segregation, which occurs across the healthy adult lifespan [43, 44]. We also found an over-recruitment of the effective connection DAN - > DMN in RS1, that can be explained by the decreased anti-correlation between DMN and DAN proven to occur in ageing at rest [45].

The posterior-anterior shift caused by the disruption within the DMN, is in line with our correlations between effective connectivity and the det-FSIQ. Indeed, the PASA model could explain that a weakened DMN - > FPL and a strengthened SN - > CING were linked to stronger IQ declines. The short-range increase of connectivity between the SN and CING seems however to contradict the findings of Onoda et al. [46], but is in line with other research [25, 31]. Indeed the salience network has proven to relate to cognitive capacity, where the within-salience connectivity was anti-correlated with fluid intelligence, and multitasking [34]. This closely resembles the short-range increased connectivity SN - > CING that correlated with the decline in cognition (FSIQ deterioration). Moreover, when concatenating RS1 and RS2 network time series, ACA showed a strong positive correlation between DMN - > FPL and the det-FSIQ, i.e., more directed connectivity from DMN to FPL would lead to less FSIQ deterioration in ACA. This is in line with the recent findings that a strengthened DMN-LFC (left frontal cortex) connectivity supports reserve (i.e., a relatively preserved cognition in disproportion to the extent of neuropathology) in mild cognitive impairment and ageing [47, 48]. Indeed, for our ACA patients, a weaker DMN - > FPL leads to a stronger cognitive deterioration, as if ACA patients' reserve capacity was not able to maintain a relatively preserved cognition. This is also in line with our cascadic hypothesis, and lack of cognitive reserve after the second 'hit' in ACA.

IQ decline in the Perceptual Reasoning Index (PRI) is mainly correlated with DMN and the (ventral) attention network dynamics. More specifically, the stronger the Granger causality from DMN to VAN there is, the more deterioration in fluid IQ is expected (Figure 5B). It has been shown that between-network connectivity with DMN is challenged with ageing, and it is associated with sharpening of the boundaries of the default mode network, and integration of the insula and cingulate with fronto-parietal attentional regions [49]. This is similar to our det-PRI correlation with the SN - > CING dynamic. Anderson and his colleagues also showed decreasing correlation between the default mode and attention control networks with age, which is in line with our consistent DMN - > VAN dynamics that correlated with the deterioration in PRI [49].

4.1. Limitations

In this study three major limitations are to be mentioned. First, we acknowledge that a third group of patients with epilepsy but no ACA, would have strengthened the results interpretation. Some of the (GC) effects depicted in ACA patients might be apparent because of epilepsy itself; and adding such a group could better confirm that effect seen here are solely made by the ACA comorbidity. Only few recent studies could show impaired directed causal inferences in brain connectivity [50, 51, 52]. The impaired directed connectivity was epilepsy-type dependent, and located in epileptic tissues, in an EEG study [50]; or was different from healthy controls in the subcortical-cortical connectivity, in frontal

lobe and temporal lobe epilepsy [51, 52]. The latter studies were also using resting-state fMRI but were limited in trying to shed light on impaired mechanism in focal epilepsies with significant results related to specific clinical characteristics (consciousness-impairing seizure in [51] and duration of epilepsy in [52]). Those characteristics are not relevant in our ACA case, where the cognitive decline is of importance. ACA patients are more heterogeneous in their epilepsy forms, seizure types, refractoriness, and durations (see Table 1), so our results should not reflect the effects of a specific type of epilepsy. Additionally, ACA cannot be separated from Epilepsy, since it is defined as an epileptic co-morbidity. Even though cognitive decline is seen in other degenerative disorders, such as in epilepsy dementia or Alzheimer disease, in such cases, degeneration do not only impaired fluid intelligence, but also long-term memory. We are not aware of other ageing disorder that develop similar, and quite specific, cognitive decline comorbidity.

As a second limitation, we hypothesized that the cognitive task executed prior a resting-state has an effect on the resting state the brain experienced, which is debatable. However, we want to emphasize we do not hypothesize that the task itself and its evoked dynamics could persists at rest afterwards, but rather, that brain cognitive reserve capacity is challenged [47, 53]; and that brain fatigue could still persist for a few minutes right after executing a cognitively demanding task [54]. So that the speed of communication, and the use of the (activity-related) network resources, weakened after the task. It also happens for healthy controls, but at lesser degree, as found in our study.

Thirdly, Granger causality validity in fMRI data is still debated. However, a research group simulated fMRI data and found out that GC at the fMRI level is monotonically related to GC at the neural level, i.e., GC from BOLD signals reliably detect neural GC [55]. Hence, they concluded that neural activity (or here, neural GC) changes, such as in a pathological group, can be detected from the fMRI data. But in our case, time-series are not direct BOLD signals, but indirect (BOLD-derived) network activity, so it remains uncertain that the monotonic relationship between neural GC and the network GC is fully preserved.

Overall, caution should be taken with respect to the interpretation of the effect of (network) brain dynamics on the IQ decline, and further research with a third group, an epilepsy-control group, could alleviate these limitations and uncertainties.

5. Conclusion

Accelerated cognitive ageing (ACA) in epilepsy shows decline in cognitive abilities that resemble normal processes of cognitive ageing in older subjects, but at greater speed. Comparing brain resting-state dynamics of ACA patients and age-, and education-level-matched controls, we mainly found strengthened effective connectivity between large-scale cognitive networks in ACA. This shows a tendency of over-recruitment as a compensatory mechanism, in line with the CRUNCH model for ageing. However, this seem to be a fragile mechanism that fails after cognitive load, showing an exhaustion phenomenon, corroborating our second-hit model, which describes the lack of cognitive reserve capacity in ACA patients. Furthermore, the DMN to ventral attention network directed connectivity strongly correlates with the decline in the perceptual reasoning IQ, which is in line with the PASA model. Both CRUNCH and PASA models show that the deterioration in the patients can be described as processes that are seen in older individuals, albeit in our patients at a younger age.

Declarations

Author contribution statement

A. Bernas: Conceived and designed the experiments; Performed the experiments; Conceived and designed the experiments; Performed the experiments; Wrote the paper.

L. E. M Breuer: Conceived and designed the experiments.

R. Lamerichs, A. J. A. de Louw: Contributed reagents, materials, analysis tools or data.

A. P. Aldenkamp, S. Zinger: Conceived and designed the experiments; Performed the experiments.

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The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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