NR4A1 Associated Multimodal Neuroimaging Patterns Impaired in Mesial Temporal Lobe Epilepsy

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INTRODUCTION: There is compelling evidence that mesial temporal lobe epilepsy (MTLE) is associated with aberrant DNA methylation (Miller-Delaney et al., 2014;Long et al., 2017). One example is NR4A1 gene, which was suggested to play a pivotal role in temporal lobe epilepsy and associated with seizure severity and onset latency (Zhang et al., 2016). However, the multimodal brain alterations associated with methylation of NR4A1, as well as their potential interactions with MTLE have not been examined yet (Richardson, 2010).

METHODS: Based on a goal-directed and supervised learning model called MCCAR (Multi-site Canonical Correlation Analysis with Reference) (Qi et al., 2018), we explored the interrelationships between the methylation level of NR4A1 and three types of MRI features from 56 MTLE patients and 65 age- and gender-matched healthy controls (HCs). As shown in Fig 1, prior knowledge (methylation level of NR4A1, MTLE>HC) was used as a reference to identify co-varying components that also have group-differentiating loadings between MTLE and HCs among 3 MRI features, including functional connectivity (FC) generated via brainnetome atlas from resting-state fMRI, fractional anisotropy (FA) from diffusion MRI and grey matter density (GM) from sMRI. Furthermore, correlation analyses were performed between loading parameters of each component and seizure severity or cognitive scores.

RESULTS: Fig 2(a) displayed the joint MRI components that were not only significantly group-discriminating (Two sample t-test: $p=4.8\times10^{-4}$, $p=2.3\times10^{-3}$, $p=4.2\times10^{-4}$, FDR corrected, Fig 2(b)), but also significantly correlated with the methylation level of NR4A1 ($r=0.40$, $r=0.40$, $r=0.43$; $p<5\times10^{-4}$) respectively. Results showed that higher methylation levels of NR4A1 in the blood of MTLE were associated with decreased GM in thalamus and basal ganglia, lower FA in fornix projected to

thalamus and external capsule between insular and basal ganglia, and reduced FC among thalamus, basal ganglia and insular. Moreover, aberrant temporal network activities were found in MTLE, including GM reduction in middle/ inferior temporal gyrus and temporal pole, lower FA in cingulum (hippocampus) and inferior longitudinal fasciculus connected to temporal pole, as well as reduced FC between temporal lobe and inferior parietal lobe, cerebellum. Results also exhibited reduced GM in cerebellum, lower FA in middle cerebellar peduncle and decreased FC between cerebellum and middle temporal gyrus, occipital lobe in MTLE. In addition, reduced FA in corpus callosum was also found in MTLE, as well as more than half dysconnectivity between right and left regions. The above results were consistent with (McDonald et al., 2008;Maccotta et al., 2013;Scanlon et al., 2013). Finally, the identified components were negatively correlated with age of onset (P=-0.62, P=-0.65, P=-0.58) in MTLE and cognitive performance measured by minimum mental state examination (MMSE, P=-0.34, P=-0.43, P=-0.35, Fig 2(d) and (e)).

CONCLUSIONS: This is the first study to link the methylation of NR4A1 with multimodal human brain imaging in MTLE. Results suggested that higher methylation level in MTLE is related with multiple subcortical nucleus including thalamus and basal ganglia, temporal network especially in temporal pole, and cerebellum, which were co-varying between brain function and structure. More interestingly, the identified brain regions were correlated with MTLE age of onset and their MMSE scores, suggesting that increased methylation of NR4A1 may be linked with earlier MTLE onset, as well as more impaired cognitive ability of MTLE. In summary, by using a supervised data fusion method, we found that dysregulation of methylation of NR4A1 may affect both function and structure in MTLE, especially the subcortical nucleus, temporal network and cerebellum. This work implicated a potential imaging-methylation pathway modulated by NR4A1 which may affect MTLE and await further verification.

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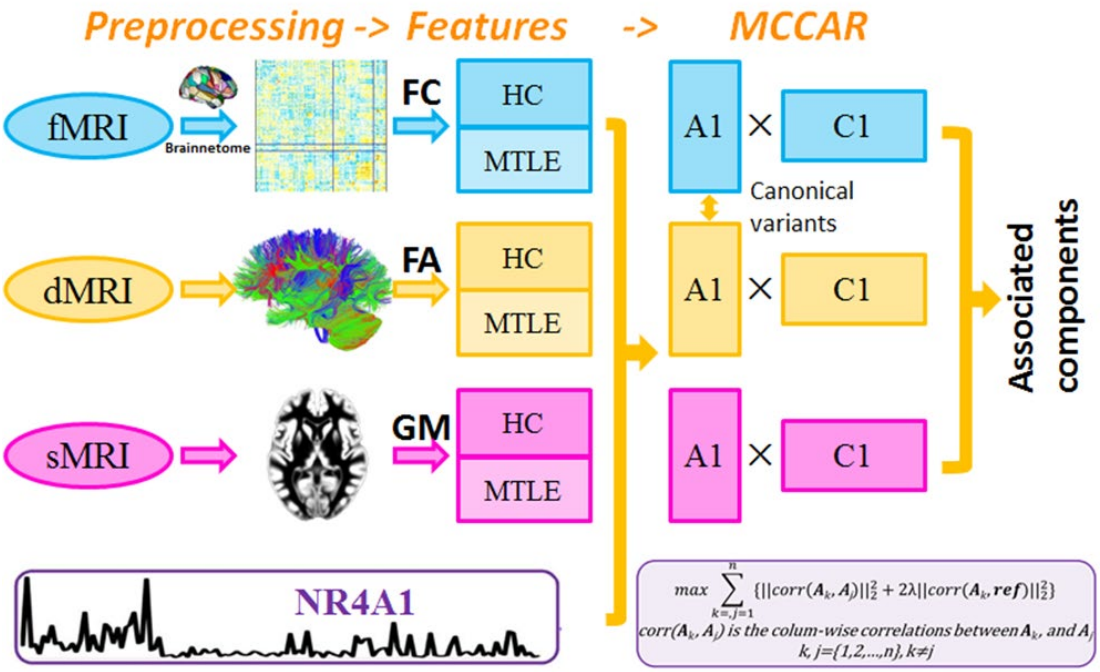

Fig 1. The flowchart of the supervised 3-way data fusion strategy (MCCAR), which simultaneously maximizes the inter-modality covariation and correlations between loadings of certain components and the reference (i.e., the methylation levels of NR4A1).

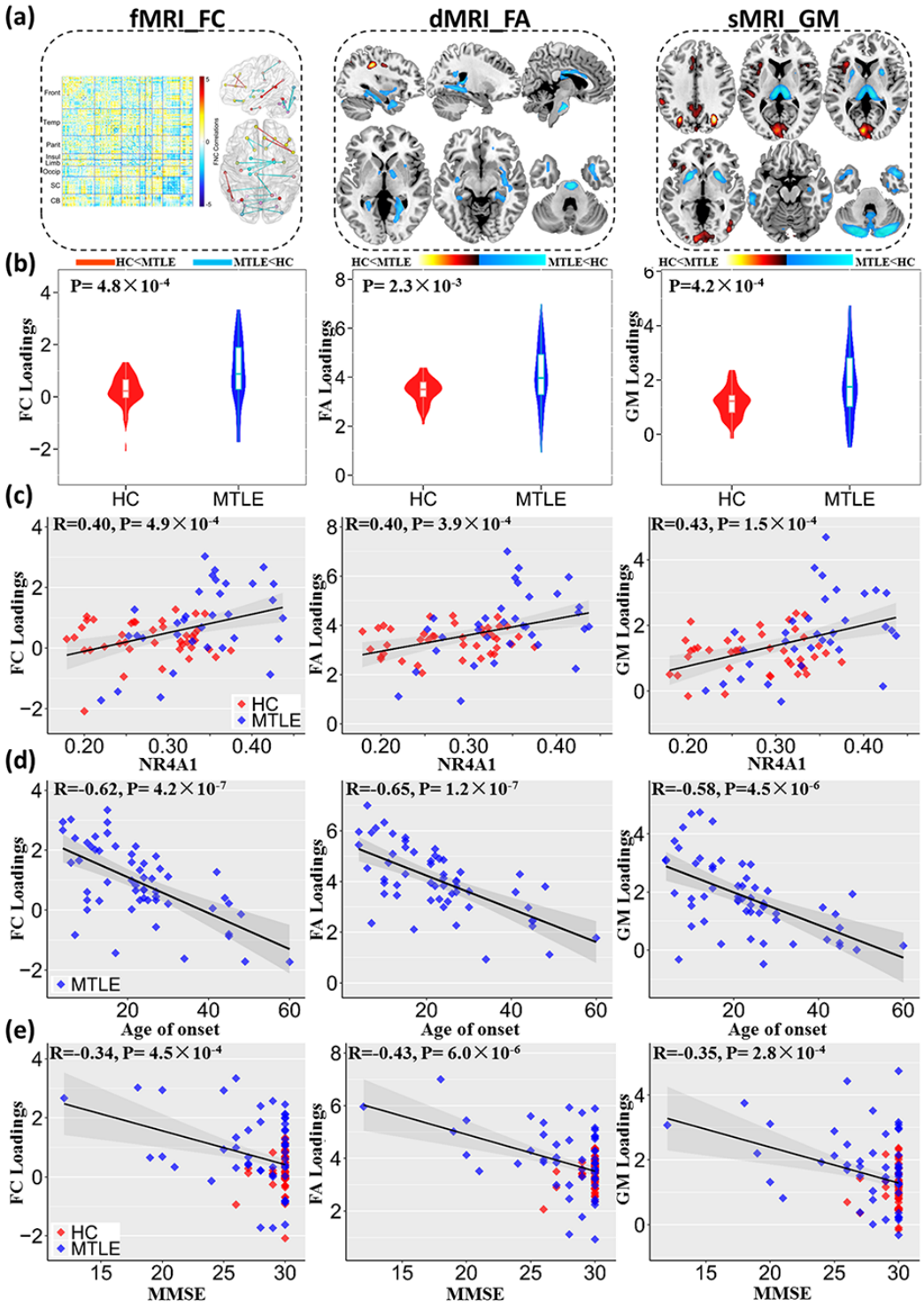

Fig 2. (a) Joint components that are significantly correlated with methylation of NR4A1. (b) Group difference of FC, FA, GM component loadings between MTLE and HCs. (c) Correlations between component loadings and the methylation levels of NR4A1. (d) Correlations between component loadings and age of onset in MTLE. (e) Correlations between component loadings and Minimum Mental State Examination score.