Reconfiguration of Structure-Function Coupling in Diverse Subgroups of Adolescents with Depression

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INTRODUCTION: The presence of major depressive disorder (MDD) during adolescence is associated with elevated rates of self-harm and suicide, which induces significant adverse impact on brain development(Vigo et al., 2016; Vos et al., 2020). Existing findings have suggested that the neurobiological basis of depressive symptom profiles in adolescents is related to complex interactions between environment and multimodal brain development (Redlich et al., 2018; Steingard et al., 1996). However, beyond the functional or structural impairment in cortex or connectivity, whether the structure-function coupling (SC-FC coupling) is disrupted in adolescent MDD, and how such disrupted coupling differ in various MDD subgroups with different clinical characters and environmental stressors remain underexplored. To this end, this study aimed to determine how the SC-FC coupling alters in adolescents with MDD and 3 types of sub-groups.

METHODS: In this cross-sectional case-control clinical neuroimaging study, we collected the resting-state functional magnetic resonance images (fMRI) and diffusion MRI data of 187 adolescents with MDD and 120 healthy controls aged 10 to 18 years in Chongqing, China. Structure-function coupling was calculated for each brain region of each subject using whole-brain structure and function connectivity as did in (Zamani Esfahlani et al., 2022)(**Fig 1**). Primary analyses included the group differences in terms of structure-function coupling of adolescent MDD and HCs. Secondary analyses included differences among 3 types of MDD subgroups (**Fig 2**), *i.e.*, subgroups with or without **suicide attempt** (SA+ / SA−), with or without **non-suicidal self-injury** (NSSI+ / NSSI−), with or without **major life events** (MLE+ / MLE−).

RESULTS: Adolescent MDD overall showed increased structure-function coupling in visual network, post default mode network and insula (Cohen's *d* ranged from 0.411 to 0.614, p_{FDR} <.05) (**Fig 1C**). Regions with group-differed SC-FC coupling (p_{FDR} < 0.05, 246 tests) were labeled in the Manhattan plot (**Fig1D**). **Fig 1E** shows significantly increased SC-FC coupling in adolescent MDD in five anatomical structures. More importantly, we identified subgroup-specific alterations in SC-FC coupling. Particularly, the parahippocampal (A35/36c_L) coupling decreased in MDD with suicide attempt (SA+ , **Fig 2A, B**) with partial η^2 0.045, 90% CI 0.023 to 0.116, p_{FDR} = .004; while compared with NSSI+ and HC, SC-FC coupling increased in subregions of right insula (dIa_R) with partial η^2 0.057, 90% CI 0.017 to 0.104, p_{FDR} = .010, and left thalamus (cTtha_L) with partial η^2 0.059, 90% CI 0.018 to 0.106, p_{FDR} = .009) in NSSI− (**Fig 2C, D**). Remarkably, subgroup variations of SC-FC coupling were most prominent in MDD subgroups related to major life events, in which unique frontal-limbic coupling increases (*e.g.*, medial frontal gyrus (A8vl_L), orbital gyrus (A14m_L/A14m_R), and amygdala (lAmyg_R) *etc*.) were observed in MLE+ subgroup with patial η^2 ranged from 0.045 to 0.068, p_{FDR} < .05 (**Fig 2E, F**).

CONCULUSIONS: Compared to typical developed adolescent, the brain functional communications in adolescent MDD were bound more tightly by anatomical pathways, especially in default mode network, visual network, and insula, which may link to the impaired cross-network dynamics in MDD.

Furthermore, the patterns of aberrant structure-function change also interacted with the clinical characters, suggesting potential heterogeneity in neuropathology of the MDD. Collectively, the findings contribute to identification of the common and subgroup-specific neurophysiological markers in adolescent MDD, highlighting the role of adversity exposure in sculpting brain development during adolescence.

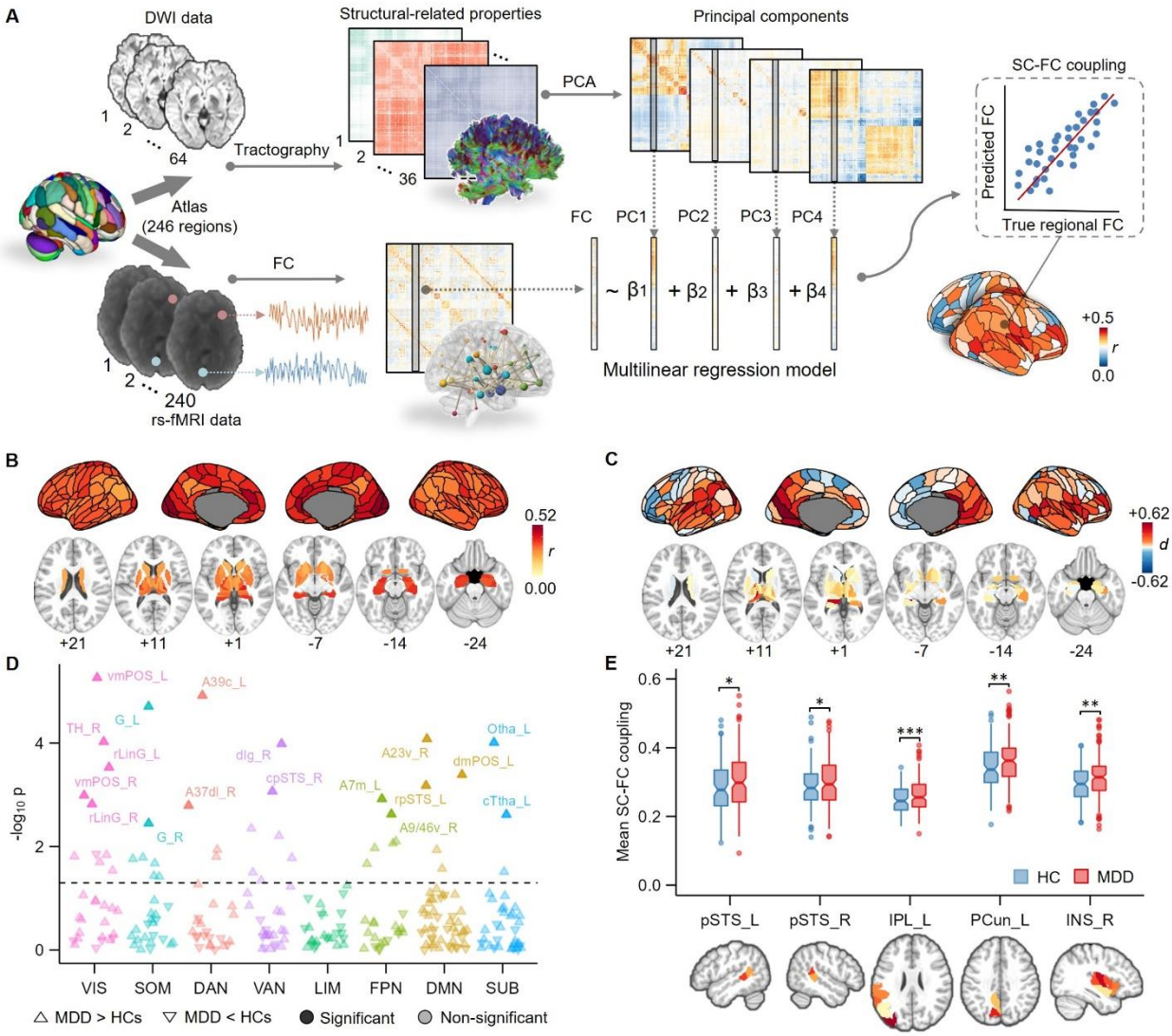

Figure 1. (**A**) The pipeline for calculating the SC-FC coupling of each brain region. (**B**) The group-averaged SC-FC coupling of HCs (n = 101). (**C**) The differences of SC-FC coupling (measured as Cohen's d) between adolescent MDD and HCs at each brain region. (**D**) Manhattan plot of SC-FC coupling differences between adolescent MDD and HCs. Regions with group-differed SC-FC coupling ($p_{FDR} < 0.05$, 246 tests) were labeled in the plot. The dashed horizontal line indicated $\log_{10}P = .05$ (uncorrected). (**E**) The mean SC-FC coupling of five anatomical structures were significantly increased in adolescent MDD ($p_{FDR} < 0.05$, 48 tests).

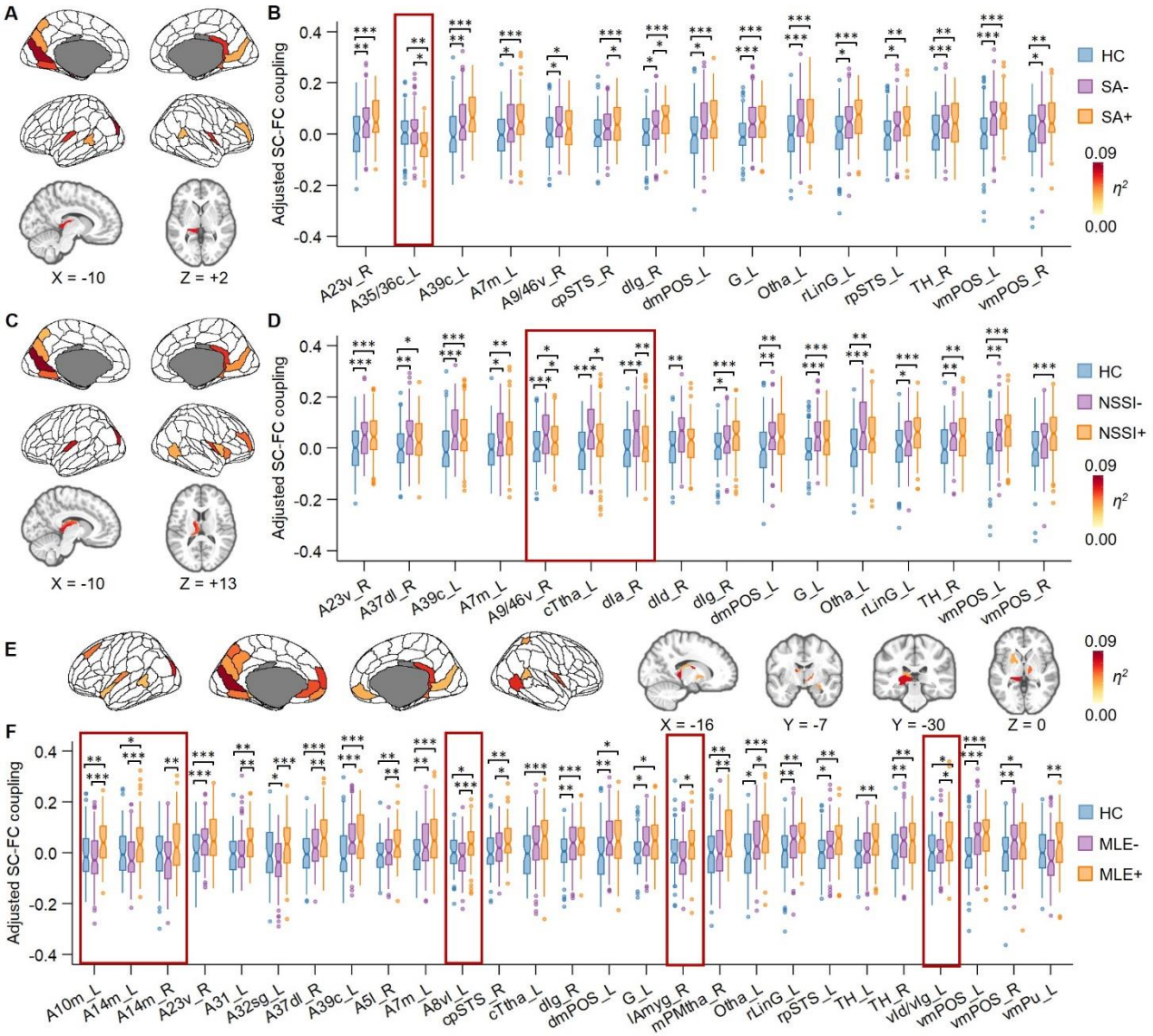

Figure 2. (**A**) Regions with significant differences of SC-FC coupling among HCs, SA+ and SA−. (**B**) *Post-hoc* comparisons of SC-FC coupling among HCs, SA+ and SA−. (**C**) Regions with significant differences of SC-FC coupling among HCs, NSSI+ and NSSI−. (**D**) *Post-hoc* comparisons of SC-FC coupling among HCs, NSSI+ and NSSI−. (**E**) Regions with significant differences of SC-FC coupling among HCs, MLE+ and MLE−. (**F**) *Post-hoc* comparisons of SC-FC coupling among HCs, MLE+ and MLE−.

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