Disrupted emotional resilience and neurovisceral integration in early small vessel disease

Olga R. Dobrushina[a, b], MD, PhD, 0000-0002-9493-4212

Larisa A. Dobrynina[a], MD, PhD, 0000-0001-9929-2725

Galina A. Arina[c], MSc, 0000-0003-1321-9354

Viktoriya V. Trubitsyna[a], MD, 0000-0001-7898-6541

Evgenia S. Novikova[a], MD, 0000-0001-5236-7259

Vlada V. Kolomoitseva[a, c], MSc, 0000-0003-1145-0739

Daria A. Alexandrova[a, c], 0000-0002-4642-6723

Elena I. Kremneva[a], MD, PhD, 0000-0001-9396-6063

Marina V. Krotenkova[a], MD, PhD, 0000-0003-3820-4554

[a] Russian Center of Neurology and Neurosciences, 80 Volokolamskoe, Moscow, Russia, 125367

[b] University of Strathclyde, Department of Psychological Sciences & Health, 40 George Street, Glasgow, UK, G1 1QE

[c] Lomonosov Moscow State University, Faculty of Psychology, 11 Mochovaya, Moscow, Russia, 125009

Correspondence:
Olga Dobrushina, 40 George Street, Glasgow, UK, G1 1QE, olga.dobrushina@strath.ac.uk

Short running title: Early affective and interoceptive markers of SVD

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Abstract

Background

Cerebral small vessel disease (SVD) is a major cause of cognitive decline and late-life depression, yet its early affective markers are poorly understood. Ageing is typically associated with enhanced emotion regulation, including greater differentiation of affective states and a shift toward positivity. Whether SVD disrupts these resilience mechanisms before overt clinical impairment is unknown.

Methods

Eighty-two adults were studied: young (n=22) and middle-aged (n=23) adults without brain abnormalities, and middle-aged adults with early SVD (n=37). Participants completed an ecologically grounded social emotion fMRI paradigm and self-report questionnaires of interoceptive and emotional awareness. Group differences in emotional differentiation, positivity, and neurovisceral integration were analysed to assess the effects of healthy ageing and early SVD.

Results

Compared with young adults, middle-aged adults without SVD showed preserved emotional differentiation, positivity bias, and intact neurovisceral integration. In contrast, early SVD was associated with reduced emotional differentiation, loss of the age-related positivity effect, and altered insular encoding of arousal. Impaired neurovisceral integration translated into diminished heart rate adaptation during sustained emotional processing. Self-report alexithymia ratings and interoceptive profiles further indicated reduced emotional awareness and embodied self-regulation in adults with SVD. These effects persisted after adjustment for cognition, cardiovascular risk factors, depression, and anxiety.

Conclusions

Early SVD is associated with affective–interoceptive disintegration evident across behavioural, neural, and physiological levels. Altered embodied regulation of emotion may constitute an early marker of vascular brain injury and a target for preventative interventions.

Introduction

Beyond physical and cognitive decline, ageing also brings gains in emotion regulation that support mental health in the face of life changes. Throughout adulthood, emotion regulation evolves to be more context-sensitive and effective, leading to a more differentiated, adaptive use of strategies (1). With a shift in motivation towards meaningful experiences, the overall emotional tone changes to more positive, a phenomenon known as the age-related positivity effect (2). In line with this growing emotional resilience, the burden of common mental disorders such as depression and anxiety typically declines from early to late adulthood (3).

This adaptive ageing trajectory, however, may be disrupted by cerebral small vessel disease (SVD), a common vascular condition that affects white matter integrity and results in mild cognitive impairment and dementia (4). The prevalence of SVD increases with age, reaching nearly 100% by age 90, making it a key contributor to mental well-being as life expectancy rises (5). SVD is not only a major cause of age-related cognitive decline, but also a mechanism of progressive depression (6,7). Depression in SVD is a direct consequence of brain injury that reduces quality of life independently of the cognitive decline (6,8). Moreover, as a well-established cardiovascular risk factor (9,10), depression might exacerbate the vascular pathology and create a vicious cycle of emotional, cerebrovascular, and cognitive decline (Dobrushina et al., 2025). Yet, despite strong links between SVD and mood disorders, most research has focused on cognition, leaving the affective domain largely unexplored.

The current study examines antecedents of mood disorders in SVD to characterise preclinical emotional vulnerability and enable preventative intervention before irreversible structural damage occurs. To address this, we adopt a framework that views emotion regulation as a mind–body process, grounded in interoception and supported by distributed neural circuits linking the insula, prefrontal cortex, and brainstem (12,13). Disruption of these circuits may impair self-regulation in social contexts, constituting a transdiagnostic vulnerability for psychiatric disorders (14). Our prior work showed that in older adults, emotional awareness correlates with the functional engagement of interoceptive networks during cardioception and is linked to preserved white-matter integrity (15,16). On the network level, emotional dysregulation in SVD is underpinned by the connectivity of the salience network (11). In a longitudinal study, nocturnal heart rate variability was predictive of four-year SVD progression (17).

Together, prior findings suggest that affective–interoceptive disintegration may serve as an early marker of vascular brain injury. Here, we test this hypothesis through a novel, ecologically grounded social emotion functional magnetic resonance imaging (fMRI) paradigm.

Methods and Materials

Study Design

A cross-sectional study included three groups of adults: young adults with no brain abnormalities (young SVD−), middle-aged adults with no brain abnormalities (middle-aged SVD−), and middle-aged adults with early small vessel disease (middle-aged SVD+). Within two weeks, participants underwent clinical evaluation, structural neuroimaging, functional magnetic resonance imaging (fMRI) with the social emotion task, and cognitive assessment.

The sample size was established to enable whole-brain analyses of continuous variables across the entire sample and between-group comparisons using region-of-interest (ROI) data. Since the fMRI task was novel, the target sample size was guided by recommendations from the neuroimaging literature, which suggests that 60–80 participants are needed to detect moderate effects in whole-brain analyses (18), and that ROI analyses can be adequately powered with smaller samples of 20–25 participants (19).

The study protocol was approved by the Ethics Committee and the Institutional Review Board of the Research Center of Neurology (protocols 4-6/19, 1-3/20, and 4-3/21), and all participants gave written informed consent. The study was not pre-registered. The data supporting the article are available from the corresponding author on request.

Participants

Inclusion criteria. Three groups were defined by age (young vs. middle-aged) and SVD status (absent vs. present): young SVD– (18–39 years), middle-aged SVD– (40–65 years), and middle-aged SVD+ (40–65 years with early SVD).

Small vessel disease status was assessed using T2 (0.68×0.68×3 mm), sagittal 3D-T2 FLAIR (1×1×1 mm), and sagittal T1 MPRAGE (1×1×1 mm) sequences, evaluated by a radiologist. Early SVD was defined as a modified Fazekas score of 1 or 2 and intact functional independence (20). The Fazekas score reflects periventricular and deep white matter lesion severity: 0 – absent, 1 – small/focal, 2 – larger with some bridging, 3 – confluent or ≥20 mm lesions (21).

Exclusion criteria. History of cardiovascular events, such as stroke or myocardial infarction, cancer or systemic diseases, endocrine diseases other than mild hypothyroidism or type 2 diabetes managed without insulin, dementia, Fazekas score 3, and structural brain abnormalities apart from SVD, including signs of neurodegenerative diseases.

Recruitment. Participants were recruited in Moscow, Russia, between 2020 and 2022. Young and middle-aged SVD− adults were enrolled from the community via researchers' social networks. Middle-aged SVD+ adults were sourced through both social networks and the Research Center of Neurology and Neurosciences database of patients with cerebrovascular conditions.

Clinical Evaluation

At enrolment, study participants were evaluated by a neurologist to collect medical history, including the absence of exclusion criteria and the presence or absence of arterial hypertension. In addition, middle-aged adults underwent 24-hour ambulatory blood pressure monitoring. Arterial hypertension was defined as the existence of a previously established diagnosis, antihypertensive medications intake, or mean systolic 24-hour ambulatory blood pressure ≥130 mmHg, or mean diastolic 24-hour ambulatory blood pressure ≥80 mmHg—in accordance with the ESC/ESH guidelines (22).

Participants completed the Toronto Alexithymia Scale (TAS-20) (23,24), Multidimensional Assessment of Interoceptive Awareness (MAIA-2) (25), Beck Depression Inventory (BDI) (26,27), and the State Trait Anxiety Inventory (28). Cognitive assessment was performed using the Montreal Cognitive Assessment, Rey-Osterrieth Complex Figure Test, Luria's Memory Word Test, Verbal Fluency Test (number of words produced in 1 minute for words beginning with "S", "B", and animal names), Stroop Test, Trail Making Test, and Tower of London Test (29–32). Questionnaires and tests were administered in Russian, using previously adapted versions.

Neuroimaging Data Acquisition and Preprocessing

Social emotion task. Participants completed a social emotion task comprising alternating 24 Emotion and 12 Pixel blocks (Figure 1). Emotion blocks presented 2–5 s videos of actors expressing anger, irritation, joy, or pleasure, followed by valence and arousal ratings. Pixel blocks displayed pixelated versions of the same videos with a noise soundtrack, followed by perceptual ratings. Stimuli were drawn from the GEMEP corpus (33) and presented using Cogent (MATLAB) on a Philips SensaVue screen. Participants responded by pressing a button with their dominant hand.

Data acquisition. Neuroimaging was performed using a Siemens MAGNETOM Prisma 3T scanner with a 20-channel coil and a Philips InVivo Functional Imaging System. Functional images were acquired using T2*-gradient echo imaging sequences (TR 2000 ms, TE 21 ms, voxel size 2×2×2 mm, FOV 192×110 mm). The scan lasted 864 seconds and comprised 432 volumes. A gradient echo field map was acquired for distortion correction (TR = 520 ms, TE1 = 4.92 ms, TE2 = 7.38 ms, voxel size = 2×2×2 mm). Pulse data were recorded simultaneously from a pulse oximeter located on the participant's non-dominant hand using the built-in Siemens Physiological Measurement Unit. Due to incomplete backup following a console malfunction, pulse data from seven participants were lost (middle-aged SVD+: 6;

middle-aged SVD−: 1). A sagittal T1 MPRAGE sequence (TR 2300 msec, TE 2.98 msec, voxel size 1×1×1 mm, FOV 256×248 mm) was used as an anatomical reference and for grey matter volume evaluation.

Data preprocessing. fMRI data were processed using SPM12 in Matlab. A standard pipeline included slice-timing correction, calculation of the voxel displacement map, realignment and unwrapping of the functional images, co-registration of the structural and functional images, spatial normalisation into standard Montreal Neurological Institute (MNI) space, and spatial smoothing using a Gaussian kernel of 8 mm full width at half maximum. Grey matter and total intracranial volumes were calculated using the CAT12 toolbox, which performs tissue segmentation and spatial normalisation via a unified approach (34).

Data Analysis

Analysis of Behavioural Data. Data analysis and visualisation were performed in R Project using packages 'dplyr', 'tidyr', 'purrr', 'lme4', 'lmerTest', 'emmeans', 'Hmisc', 'corrplot', 'RcmdrMisc', 'MASS', 'ggplot2', 'ggpubr', 'ggbeeswarm', 'ggrain', 'grid', 'gridExtra', 'cowplot', 'ggsignif'.

Emotional differentiation and *positivity* scores were calculated based on ratings from the social emotion task. Emotional differentiation was operationalised as the variance in absolute arousal and valence ratings across trials, reflecting the extent to which emotional experience was nuanced rather than confined to broad categories such as 'strong' or 'positive'. Positivity was defined by mean valence across trials.

Group differences were assessed using ANOVA, Kruskal–Wallis, or chi-square tests for normally distributed, non-normally distributed, and categorical variables, respectively, yielding an overall p-value. Pairwise post hoc comparisons focused on the effects of ageing (young vs. middle-age SVD−) and SVD (middle-age SVD− vs. SVD+), using Tukey's HSD, Wilcoxon rank-sum, or Fisher's exact tests as appropriate. Post hoc *p*-values were corrected using the false discovery rate method (*p*-FDR).

First and Second-Level fMRI Analysis. During first-level analysis, Emotion and Pixel conditions were modelled as short blocks aligned to the onset and duration of each video. Realignment parameters and physiological noise regressors were included as covariates. Activation maps were computed for the Emotion > Pixel contrast and for parametric modulation of Emotion blocks by arousal and valence ratings.

Second-level 'Emotion > Pixel', 'Arousal', and 'Valence' activation maps were inspected to assess task validity (see Supplement). To examine neural correlates of emotional differentiation and positivity, these variables were entered as second-level covariates in the 'Emotion > Pixel' contrast. Mean valence was winsorized to reduce the influence of outliers. Voxel-level threshold was set at $p < .001$, with clusters considered significant at p-FDR < .05. Fragmented results were additionally explored at voxel-level $p < .005$ with a minimum cluster size of 50 voxels. Analyses were restricted to a grey matter mask.

Neurovisceral Integration. To evaluate neurovisceral integration, right ventral anterior insula ROI data were extracted using MarsBaR from the arousal individual-level parametric modulation contrast (Figure S3). The ROI was defined by intersecting the thresholded group-level 'Arousal' activation map with the right ventral anterior insula region from the Deen et al. insula parcellation atlas (35). This region was selected based on our previous findings linking insular activation during heartbeat detection to early SVD (16) and evidence that the right ventral anterior insula encodes arousal intensity (36).

Pulse time series were processed using the TAPAS PhysIO Toolbox. For each trial, heart rate was computed as the mean within a 2–12 second window following video onset. Implausible heart rate values (below 40 bpm or above 120 bpm) were excluded, followed by removal of outliers defined as values exceeding 1.5×IQR below the first quartile or above the third quartile within each participant.

To examine group differences in heart rate dynamics during the task, a linear mixed-effects model was fitted with time, arousal rating, group, and their interaction as fixed effects and participant as a random effect. A second model was fitted to assess the association between BOLD modulation in the right anterior insula and heart rate dynamics, with time, insular modulation strength, and their interaction as fixed effects. In both models, heart rate was modelled as a continuous repeated measure across trials.

To assess group differences in interoceptive self-report profiles, we analysed MAIA-2 subscales using multivariate analysis of variance (MANOVA) and linear discriminant analysis (LDA). Separate comparisons were performed between young adults and SVD− middle-aged adults (effect of age), and between SVD− and SVD+ middle-aged adults (effect of SVD). MANOVA tested for multivariate group differences across eight MAIA-2 subscales. LDA was used to estimate the discriminant function and cross-validated classification accuracy, providing an interpretable profile of subscales most contributing to group differentiation.

Results

Participants

The study included 82 participants across three groups defined by age and SVD status (Table 1): 22 young adults without brain abnormalities (young SVD−), 23 middle-aged adults without SVD (middle-aged SVD−), and 37 middle-aged adults with early-stage SVD (middle-aged SVD+; Fazekas 1: 32; Fazekas 2: 5). The sample included more females among middle-aged adults, reflecting greater willingness to participate and the demographic profile of the recruitment database. All participants identified as White. The two middle-aged groups were matched on general cognitive ability, depressive symptoms, presence of arterial hypertension, and body mass index (BMI).

Emotional differentiation sustained in healthy ageing, altered in early small vessel disease

Groups differed in their ability to differentiate emotional experiences during the social emotion fMRI task. Middle-aged adults with SVD showed lower emotional differentiation compared to those without SVD ($\chi^2 = 6.27$, $p = .044$; p-FDR = .042 for SVD− vs. SVD+; Figure 2A), suggesting a disruption in emotional granularity. These experimental findings were mirrored in self-reported emotional insight. On TAS-20, which measures difficulties in identifying and describing emotions, the middle-aged SVD− group scored lower than both young and middle-aged SVD+ adults ($F = 5.64$, $p = .005$; p-FDR = .046 and .003, respectively; Figure 2B), consistent with better emotional self-awareness.

To understand the neural basis of these differences, we examined functional activation patterns associated with emotional differentiation (Emotion > Pixel contrast, second-level covariate analysis). At a conservative voxel-wise threshold of $p < .001$, several small clusters emerged in the prefrontal cortex, though none survived cluster-level correction (Figure 2C). When the threshold was lowered to $p < .005$, a distributed pattern of activation was observed across the bilateral prefrontal cortex (Figure 2D), forming an extended cluster of 2,051 voxels (16,408 mm^3) at cluster-level p-FDR < .0001 with activation peaks in the right orbitofrontal cortex (30, 42, −8), right lateral prefrontal cortex (34, 60, 4), and left lateral prefrontal cortex (−22, 60, 12). This suggests that fine-grained emotional differentiation, disrupted in early SVD, may be supported by a distributed prefrontal network.

Positivity effect observed in healthy ageing, not early small vessel disease

Middle-aged adults without SVD labelled their emotional experiences more positively compared to both young and middle-aged SVD+ adults. This was reflected in the mean valence ratings during the social emotion task, which differed significantly across groups ($\chi^2 = 11.74$, $p = .003$), with higher ratings in the SVD− group (p-FDR = .004 vs. young; p-FDR = .023 vs. SVD+; Figure 3A). Closer examination of the valence rating distributions (Figure 3B) revealed that young adults gave more negative and fewer positive ratings than SVD− middle-aged adults (p-FDR = .033 and .038, respectively), while SVD+ middle-aged adults gave more negative ratings than those without SVD (p-FDR = .016), but did not differ in positive ratings (p-FDR = .788). Notably, only the middle-aged SVD− group showed a reliable shift toward more positive responses overall ($p = .0002$), consistent with the age-related positivity effect.(2)

Second-level covariate analysis (Emotion > Pixel contrast) did not identify significant clusters linked to mean valence ratings at the whole-brain level. Exploratory voxel-wise analyses revealed a fragmented and spatially diffuse pattern of activation across the prefrontal cortex, particularly at more liberal statistical thresholds (Figure 3C and D), suggesting that the neural correlates of emotional valence may be subtle and distributed or exhibit high inter-individual variability.

Preserved neurovisceral integration in healthy ageing, disrupted in early small vessel disease

To assess neurovisceral integration, we examined how subjective arousal modulated BOLD responses in the right ventral anterior insula using a first-level parametric modulation analysis (Figure 4A). Modulation strength differed across groups (Kruskal–Wallis $\chi^2 = 6.19$, $p = .045$; Figure 4B). Among middle-aged adults, those with SVD showed weaker insular encoding of arousal (p-FDR = .019), suggesting disrupted affective-interoceptive integration. The difference between young and middle-aged SVD− adults was not significant (p-FDR = .164), indicating that ageing alone does not account for this mechanism. Importantly, individuals with stronger insular encoding of arousal also exhibited a more marked decrease in heart rate throughout the task ($\beta = -0.006$, $p < .001$; Table 2), linking intact neurovisceral integration to more effective physiological adaptation.

A linear mixed-effects model was used to examine how age and SVD status influenced heart rate dynamics, including group, subjective arousal, and their interactions (Table 2). Across all participants, heart rate decreased over time ($\beta = -0.003$, $p = .003$), consistent with physiological adaptation. This dynamic was reversed in middle-aged adults with SVD, who showed a significant positive time-by-group interaction ($\beta = 0.004$, $p = .005$), indicating an increase in heart rate over the task duration (Figure 4C). No significant differences in heart rate dynamics were observed between young and middle-aged SVD− adults. A significant three-way interaction was found between arousal, time, and the middle-aged SVD+ group ($\beta = 0.002$, p = .024), suggesting diminished habituation to arousing emotional stimuli in SVD.

To explore differences in interoceptive self-report profiles, we applied LDA and multivariate testing to MAIA-2 subscales. No significant multivariate differences were observed between young and middle-aged SVD− adults (Wilks' $\lambda = 0.749$, $p = .189$), and classification accuracy was low (56%). In contrast, interoceptive profiles of middle-aged SVD+ adults differed from those without SVD (Wilks' $\lambda = 0.707$, $p = .017$), with a classification accuracy of 68%. The discriminant function revealed that the most distinguishing features were reduced *attention regulation* and *emotional awareness*, as well as elevated *self-regulation* and *noticing* (Figure 4D). These findings suggest that small vessel disease is associated with a shift in interoceptive experience that is not attributable to ageing alone and may reflect an emerging disruption in self-regulatory interoceptive processing.

Group differences persist after accounting for gender, clinical, and cognitive factors

To determine whether the observed group differences could be explained by other demographic, clinical, or cognitive variables, we conducted a series of exploratory analyses.

Gender was not associated with emotional differentiation, positivity, or neurovisceral integration (Table 3), suggesting that the gender imbalance between groups did not contribute to the findings. Arterial hypertension, similarly to SVD, was linked to lower self-reported ability to regulate interoceptive attention (Table 4), but showed no significant associations with other measures of interest. Multivariate group differences in interoceptive profiles remained significant after adjusting for arterial hypertension (Wilks' $\lambda = 0.691$, $p = .014$), which itself was no longer a significant predictor (Wilks' $\lambda = .756$, $p = .070$). This suggests that the interoceptive alterations observed in SVD are not explained by comorbid vascular risk.

BDI and trait anxiety scores were correlated with alexithymia (Figure 5). However, post hoc models showed no significant main effects or interactions with group, indicating these affective symptoms did not account for the group differences. BMI was unrelated to the variables of interest, while grey matter volume showed a weak negative correlation with positivity, which did not retain in post hoc modelling.

In the cognitive examination, middle-aged SVD+ vs. SVD− adults scored lower in the Rey-Osterrieth Complex Figure Test (delayed recall), Verbal Fluency, and Trail Making tests (Table 5). Since verbal fluency was also associated with emotional differentiation, alexithymia and insular modulation of arousal (Figure 5), we tested whether it might explain the group effects. For both emotional differentiation and alexithymia, verbal fluency showed no significant main or interaction effects ($p > .39$). For insular

modulation, an interaction between group and verbal fluency was observed ($t = 2.14$, $p = .037$). However, the group effect remained significant ($t = -2.38$, $p = .021$), suggesting that verbal fluency moderated, but did not mediate, the group difference.

Discussion

The study characterises the affective signature of early SVD, distinguishing it from healthy ageing. Early SVD was marked by reduced emotional differentiation, loss of the age-related positivity effect, and impaired neurovisceral integration, together indicating diminished emotional resilience. These alterations preceded clinically significant depression or cognitive decline, representing early markers of vulnerability.

Emotional differentiation, measured as a nuanced rating of emotional experiences during the fMRI task, was preserved in healthy ageing but reduced in SVD (Figure 2). On the alexithymia scale, middle-aged adults with SVD reported difficulties understanding emotions in daily life, whereas those without SVD outperformed younger adults. Fine-grained awareness of one's emotions is a protective factor for mental health, as it enables differentiated use of self-regulation strategies (37,38). Aligned with this perspective, we observed engagement of the prefrontal cortex in participants with higher emotional differentiation, indicative of better top-down regulation. Distributed bilateral activation across lateral and orbitofrontal prefrontal regions, evident at a more liberal threshold, may reflect the diversity of neural representations underlying different emotion regulation strategies (39).

Middle-aged adults without SVD showed the typical *age-related positivity effect*, in contrast to those with emerging cerebrovascular injury (Figure 3). This difference was driven by an increased number of negative ratings in adults with SVD. The age-related positivity reflects an adaptive motivational shift as individuals confront shorter time horizons (40). Neurobiologically, it has been linked to top-down modulation of negative affect, reliant on cognitive control resources and mediated by medial prefrontal regions (41,42). Positive attitudes toward ageing are further associated with higher life satisfaction and better self-reported physical and mental health (43). The failure to suppress negativity in SVD may therefore signal early disruption to the emotion regulation mechanism that normally supports resilience in later life.

Beyond emotional changes, SVD affected interoceptive processing, including impaired *neurovisceral integration* (Figure 4). SVD, but not healthy ageing, was associated with reduced arousal modulation by the right ventral anterior insula. This region encodes arousal intensity and functions as a lower-level component of the hierarchical network that integrates interoceptive information into multimodal representations of emotional states and enables differentiated self-regulation (36). Impaired insular processing of interoceptive information was associated with diminished psychophysiological adaptation during emotional processing. Participants with SVD, unlike other groups, showed a progressive increase in heart rate throughout the social emotion task and reduced habituation to arousing social stimuli. Experimental evidence of altered neurovisceral integration was paralleled by changes in self-report interoceptive profiles. Middle-aged adults with SVD showed a shift from embodied attention regulation and emotional awareness to more effortful, detached, top-down strategies of self-regulation.

Overall, early vascular brain injury compromised differentiated, embodied regulation of emotion across behavioural, neural, and physiological levels. These associations were independent of gender, cardiovascular risk factors such as hypertension and BMI, cognitive decline, or mood and anxiety disorders (Tables 3, 4, and 5; Figure 5). Notably, verbal fluency moderated the relationship between vascular brain injury and insular modulation of arousal, consistent with our earlier observation of reduced resting-state connectivity between the salience and language networks in SVD-related emotional dysregulation (11). This finding may reflect the critical role of verbal mediation in emotional-interoceptive regulation (44) and point to a trajectory in which advancing cognitive decline further undermines emotional resilience.

Due to the cross-sectional nature of the study, it remains unclear whether the observed differences between middle-aged adults with and without SVD were secondary to emerging brain injury, reflected a trait vulnerability that predisposed to SVD, or a combination of both. This limitation could be addressed by longitudinal studies. Future research should also explore other aspects of emotional resilience, particularly those related to real-life environments, social roles, and interpersonal relationships, which are especially relevant in older age (45). Finally, studies should aim for more demographically balanced and ethnically diverse samples to enhance generalisability.

This study advances understanding of age-related vascular brain injury and its affective mechanisms. To our knowledge, this is the first comprehensive characterisation of the emotional–interoceptive signature in early SVD. Experimental findings from an ecologically grounded fMRI task, paralleled by self-reports of daily functioning, indicate pervasive alterations with direct relevance to real-world contexts. Disruption of emotional differentiation, positivity, and neurovisceral integration may represent mechanistic pathways to SVD-related depression and constitute candidate biomarkers of emerging vascular brain injury. These alterations also highlight targets for behavioural and neurophysiological interventions to prevent progression to vascular injury, cognitive decline, and depression (46–49). Ultimately, this work delineates a translational avenue for early intervention to preserve resilience and mental health across the lifespan.

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Disclosures

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Table 1. Characteristics of the Study Sample

Variable	Statistics	Young SVD− (N=22)	Middle-aged SVD− (N=23)	Middle-aged SVD+ (N=37)
Age (years)	N_{obs} (N_{miss})	22 (0)	23 (0)	37 (0)
	Mean±SD	28.73±6.98	52.83±4.49	54.76±6.05
	Median [IQR]	31.00 [20.25, 34.75]	53.00 [50.00, 56.00]	5.00 [51.00, 59.00]
	Range	(19.00, 39.00)	(45.00, 60.00)	(40.00, 64.00)
	Overall *p*-value	< .001		
	Pairwise *p*-FDR		< .001	.224
Gender	N_{obs} (N_{miss})	22 (0)	23 (0)	37 (0)
Female	N (%)	10 (45.45%)	16 (69.57%)	31 (83.78%)
Male	N (%)	12 (54.55%)	7 (30.43%)	6 (16.22%)
	Overall *p*-value	.008		
	Pairwise *p*-FDR		.215	.215
Arterial hypertension	N (%)	22 (0)	23 (0)	36 (1)
Absent	N (%)	22 (100.00%)	11 (47.83%)	19 (52.78%)
Treated (controlled)	N (%)	0 (0.00%)	4 (17.39%)	3 (8.57%)
Treated (uncontrolled)	N (%)	0 (0.00%)	5 (21.74%)	4 (11.43%)
Untreated	N (%)	0 (0.00%)	3 (13.04%)	8 (22.22%)
	Overall *p* (presence)	< .001		
	Pairwise *p*-FDR		< .001	.791
Mean 24-hour systolic blood pressure	N_{obs} (N_{miss})	0 (22)	23 (0)	32 (5)
	Mean±SD		117.50±13.49	117.89±14.00
	Median [IQR]		115.90 [109.95, 126.50]	117.80 [107.13, 127.10]
	Range		(95.70, 153.60)	(94.70, 147.30)
	p-value			.919
Mean 24-hour diastolic blood pressure	N_{obs} (N_{miss})	0 (22)	23 (0)	32 (5)
	Mean (SD)		76.43±9.58	78.56±15.94
	Median [IQR]		75.20 [70.60, 81.75]	75.80 [69.10, 83.70]
	Range		(59.90, 103.60)	(54.00, 146.80)
	p-value			.571
Grey matter volume, percent of total intracranial volume	N_{obs} (N_{miss})	22 (0)	23 (0)	37 (0)
	Mean±SD	45.58±2.88	41.84±1.72	42.31±1.98
	Median [IQR]	45.68 [44.04, 47.71]	41.77 [40.75, 42.87]	42.48 [41.11, 43.42]
	Range	(39.94, 51.29)	(37.85, 45.36)	(38.07, 46.94)
	Overall *p*-value	< .001		
	Pairwise *p*-FDR		< .001	.326
BMI	N_{obs} (N_{miss})	22 (0)	23 (0)	37 (0)
	Mean±SD	22.89±4.15	27.91±5.31	27.36±4.93
	Median [IQR]	21.93 [19.47, 26.01]	27.85 [24.22, 31.75]	27.17 [24.52, 30.12]
	Range	(17.71, 30.97)	(19.57, 39.04)	(18.52, 39.01)
	Overall *p*-value	<.001		
	Pairwise *p*-FDR		.003	.676
MOCA	N_{obs} (N_{miss})	0 (22)	23 (0)	35 (2)
	Mean±SD		26.70±1.99	25.89±2.27
	Median [IQR]		27.00 [25.00, 28.50]	26.00 [25.00, 27.00]
	Range		(23.00, 29.00)	(20.00, 30.00)
	Overall *p*-value	.225		
TAS-20	N_{obs} (N_{miss})	22 (0)	23 (0)	37 (0)
Score	Mean±SD	45.05±13.35	38.04±9.72	48.32±11.47
	Median [IQR]	44.00 [33.75, 56.25]	39.00 [31.00, 42.50]	49.00 [40.00, 57.00]
	Range	(24.00, 69.00)	(23.00, 58.00)	(21.00, 70.00)
Possible alexithymia (52–60)	N (%)	2 (9.09%)	3 (13.04%)	9 (24.32%)
Alexithymia (≥ 61)	N (%)	4 (18.18%)	0 (0.00%)	5 (13.51%)
	Overall *p*-value	.005		
	Pairwise *p*-FDR		.046	.003

BDI	N_{obs} (N_{miss})	22 (0)	23 (0)	37 (0)
Score	Mean (SD)	7.55±5.63	7.91±5.72	9.92±7.77
	Median [IQR]	5.50 [4.00, 10.00]	7.00 [3.00, 12.00]	8.00 [4.00, 15.00]
	Range	(0.00, 21.00)	(0.00, 24.00)	(0.00, 33.00)
Mild depression (10–18)	N (%)	5 (22.73%)	7 (30.43%)	13 (35.14%)
Moderate depression (19–29)	N (%)	2 (9.09%)	1 (4.35%)	4 (10.81%)
Severe depression (≥ 30)	N (%)	0 (0.00%)	0 (0.00%)	1 (2.70%)
	Overall *p*-value	.532		
STAI Trait	N_{obs} (N_{miss})	22 (0)	23 (0)	37 (0)
Score	Mean (SD)	44.68±9.03	45.30±8.35	50.38±9.50
	Median [IQR]	45.00 [37.50, 51.75]	44.00 [39.50, 49.50]	51.00 [45.00, 58.00]
	Range	(25.00, 58.00)	(35.00, 68.00)	(28.00, 65.00)
Moderate anxiety (38–44)	N (%)	5 (22.73%)	7 (30.43%)	5 (13.51%)
High anxiety (≥ 45)	N (%)	11 (50.00%)	11 (47.83%)	28 (75.68%)
	Overall *p*-value	.032		
	Pairwise *p*-FDR		.819	.077

Note that the Russian version of the MOCA test was used, making absolute scores non-comparable to those obtained using the English version.

Table 2. Linear Mixed Model Results: Role of Insular Modulation and Group Differences in the Heart Rate Dynamics

Model	Predictor	Estimate	Std. Error	t-value	*p*-value
HR ~ Onset × InsularModulation + (1 | ID)	Intercept	68.19	1.239	55.03	<.001
	Onset	0.001	0.001	1.06	.288
	Insular modulation	4.27	2.96	1.44	.154
	Onset × Insular modulation	−0.006	0.001	−5.31	<.001
HR ~ Onset × Group + (1 | ID)*	Intercept	69.19	2.39	28.95	< .001
	Onset	−0.002	0.001	−2.24	.025
	Group: Young Adults	0.434	3.16	0.14	.891
	Group: Middle-aged SVD+	−0.645	2.88	−0.22	.824
	Onset × Young Adults	−0.001	0.002	−0.94	.348
	Onset × Middle-aged SVD+	0.003	0.001	3.15	.002

* The reference group is Middle-aged SVD−

Table 3. Role of Gender in the Effects of Interest

Variable	Statistics	Female (N=57)	Male (N=25)
Emotional differentiation	Mean±SD	0.33±0.15	0.34±0.13
	Median [IQR]	0.32 [0.22, 0.44]	0.31 [0.28, 0.43]
	Range	(0.00, 0.65)	(0.04, 0.57)
	p-value	.548	
Alexithymia (TAS-20)	Mean±SD	45.46±12.81	42.52±10.64
	Median [IQR]	45.00 [36.00, 57.00]	42.00 [35.00, 49.00]
	Range	(21.00, 70.00)	(23.00, 63.00)
	p-value	.285	
Mean valence	Mean±SD	0.08±0.26	0.09±0.31
	Median [IQR]	0.08 [−0.04, 0.29]	0.08 [−0.12, 0.33]
	Range	(−0.79, 0.67)	(−0.38, 0.71)
	p-value	.952	
Insular Modulation	Mean±SD	0.18±0.34	0.22±0.39
	Median [IQR]	0.17 [-0.01, 0.34]	0.18 [0.00, 0.46]
	Range	(−0.61, 1.49)	(−0.92, 0.95)
	p-value	.536	
Heart rate dynamics (slope)	Mean±SD	−0.02±0.16	0.02±0.10
	Median [IQR]	0.01 [-0.06, 0.08]	−0.02 [−0.05, 0.06]
	Range	(−0.54, 0.33)	(−0.14, 0.32)
	p-value	.918	
MAIA-2, Attention regulation	Mean±SD	2.67 ± 1.06	2.90 ± 0.87
	Median [IQR]	2.71 [2.00, 3.29]	3.00 [2.14, 3.43]
	Range	(0.14, 5.00)	(1.29, 5.00)
	p-value	.313	
MAIA-2, Self-regulation	Mean±SD	2.06 ± 1.35	2.25 ± 1.36
	Median [IQR]	2.00 [1.00, 3.25]	2.00 [1.00, 3.50]
	Range	(0.00, 5.00)	(0.00, 4.50)
	p-value	.579	

Table 4. Role of Arterial Hypertension in the Effects of Interest

Variable	Statistics	Middle-aged hypertension− (N=30)	Middle-aged hypertension+ (N=29)
Emotional differentiation	Mean±SD	0.33±0.12	0.31±0.16
	Median [IQR]	0.31 [0.25, 0.41]	0.31 [0.18, 0.45]
	Range	(0.11, 0.60)	(0.00, 0.65)
	p-value	.791	
Alexithymia (TAS-20)	Mean±SD	42.83±10.63	46.34±13.01
	Median [IQR]	42.00 [36.50, 50.00]	45.00 [36.00, 57.00]
	Range	(21.00, 61.00)	(23.00, 70.00)
	p-value	.262	
Mean valence	Mean±SD	0.12±0.26	0.13±0.30
	Median [IQR]	0.12 [0.01, 0.29]	0.08 [-0.04, 0.38]
	Range	(-0.79, 0.50)	(-0.42, 0.71)
	p-value	.915	
Insular Modulation	Mean±SD	0.18±0.31	0.26±0.33
	Median [IQR]	0.15 [0.01, 0.31]	0.22 [0.05, 0.53]
	Range	(-0.29, 1.49)	(-0.49, 0.95)
	p-value	.172	
Heart rate dynamics (slope)	Mean±SD	0.01±0.14	-0.01±0.13
	Median [IQR]	0.01 [-0.02, 0.06]	-0.00 [-0.06, 0.09]
	Range	(-0.54, 0.33)	(-0.38, 0.14)
	p-value	.723	
MAIA-2, Attention regulation	Mean±SD	3.03 ± 0.92	2.32 ± 0.96
	Median [IQR]	2.93 [2.57, 3.54]	2.43 [1.57, 3.00]
	Range	(0.71, 4.86)	(0.14, 4.29)
	p-value	.013	
MAIA-2, Self-regulation	Mean±SD	2.28 ± 1.45	1.75 ± 1.24
	Median [IQR]	2.12 [1.00, 3.44]	1.50 [1.00, 2.25]
	Range	(0.00, 5.00)	(0.00, 4.00)
	p-value	.176	

Table 5. Cognitive Performance Across Study Groups

Variable	Statistics	Young SVD− (N=22)	Middle-aged SVD− (N=23)	Middle-aged SVD+ (N=37)
Rey-Osterrieth Complex Figure Test, copy	N_{obs} (N_{miss})	22 (0)	23 (0)	37 (0)
	Mean±SD	35.41±1.14	35.39±0.94	34.49±2.09
	Median [IQR]	36.00 [35.25, 36.00]	36.00 [35.00, 36.00]	35.00 [34.00, 36.00]
	Range	(32.00, 36.00)	(33.00, 36.00)	(28.00, 36.00)
	Overall *p*-value	.076		
Rey-Osterrieth Complex Figure Test, delayed recall	N_{obs} (N_{miss})	22 (0)	23 (0)	37 (0)
	Mean±SD	22.82±5.50	25.80±5.04	22.00±4.73
	Median [IQR]	24.00 [19.62, 25.00]	26.00 [24.00, 29.75]	21.00 [19.00, 25.00]
	Range	(8.00, 32.00)	(14.50, 34.00)	(12.00, 33.00)
	Overall *p*-value	.021		
	Pairwise *p*-FDR		.086	.011
Luria's Memory Word Test, delayed recall	N_{obs} (N_{miss})	0 (22)	23 (0)	37 (0)
	Mean±SD		8.30±1.49	8.30±1.68
	Median [IQR]		9.00 [7.00, 9.50]	8.00 [7.00, 10.00]
	Range		(5.00, 10.00)	(3.00, 10.00)
	p-value			.864
Verbal Fluency, words	N_{obs} (N_{miss})	0 (22)	23 (0)	37 (0)
	Mean±SD		57.78±10.22	49.46±10.96
	Median [IQR]		58.00 [51.00, 64.00]	49.00 [40.00, 57.00]
	Range		(33.00, 78.00)	(33.00, 71.00)
	p-value			.005
Stroop Test, total time	N_{obs} (N_{miss})	0 (22)	23 (0)	37 (0)
	Mean±SD		167.74±28.17	181.54±29.92
	Median [IQR]		163 [143, 186]	175 [158, 196]
	Range		(132.00, 217.00)	(143.00, 270.00)
	p-value			.074
Stroop Test, total errors	N_{obs} (N_{miss})	0 (22)	23 (0)	37 (0)
	Mean±SD		2.87±2.42	4.65±4.35
	Median [IQR]		2.00 [1.00, 4.50]	3.00 [2.00, 6.00]
	Range		(0.00, 10.00)	(0.00, 18.00)
	p-value			.147
Trail Making Test, part A time	N_{obs} (N_{miss})	0 (22)	23 (0)	37 (0)
	Mean±SD		29.74±9.75	35.14±13.58 33.00
	Median [IQR]		27.00 [23.00, 36.50]	[29.00, 38.00]
	Range		(16.00, 49.00)	(20.00, 89.00)
	p-value			.050
Trail Making Test, part B time	N_{obs} (N_{miss})	0 (22)	23 (0)	37 (0)
	Mean±SD		68.17±29.58	93.54±49.09
	Median [IQR]		65.00 [46.00, 76.00]	83.00 [62.00, 107.00]
	Range		(38.00, 156.00)	(36.00, 279.00)
	p-value			.017
Trail Making Test, B/A ratio	N_{obs} (N_{miss})	0 (22)	23 (0)	37 (0)
	Mean±SD		2.36±0.81	2.76±1.32
	Median [IQR]		2.13 [1.75, 3.07]	2.34 [1.94, 3.13]
	Range		(1.24, 4.39)	(1.24, 7.54)
	p-value			.334
Tower of London, score	N_{obs} (N_{miss})	0 (22)	23 (0)	37 (0)
	Mean±SD		18.04±1.92	16.92±2.94
	Median [IQR]		18.00 [17.00, 19.00]	18.00 [15.00, 19.00]
	Range		(13.00, 22.00)	(8.00, 22.00)
	p-value			.109

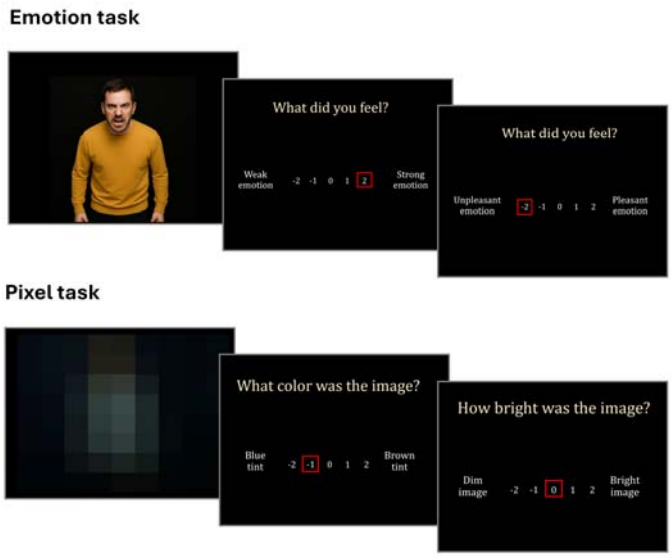

Figure 1. Social Emotion Functional MRI Task

The task included alternating Emotion and Pixel blocks (Figure 1). In Emotion blocks, participants viewed front-facing video clips (2–5 sec) of actors from the GEMEP corpus expressing anger, irritation, joy, or pleasure using both facial and upper-body expressions, accompanied by emotionally intoned pseudo-language phrases. Each video was followed by arousal and valence rating scales (8 sec each) and a fixation cross (2 sec). Pixel blocks presented spatially pixelated versions of the same videos overlaid with a white noise soundtrack; participants rated the perceived colour and brightness of the image. A total of 24 Emotion blocks (six actors × four emotions) and 12 Pixel blocks were delivered in a fixed structure: four Emotion blocks (pseudorandomized order, different actors) followed by two Pixel blocks, repeated four times.

The figure uses an AI-generated illustration of an actor instead of a GEMEP image, as the corpus does not permit publication of the original stimuli.

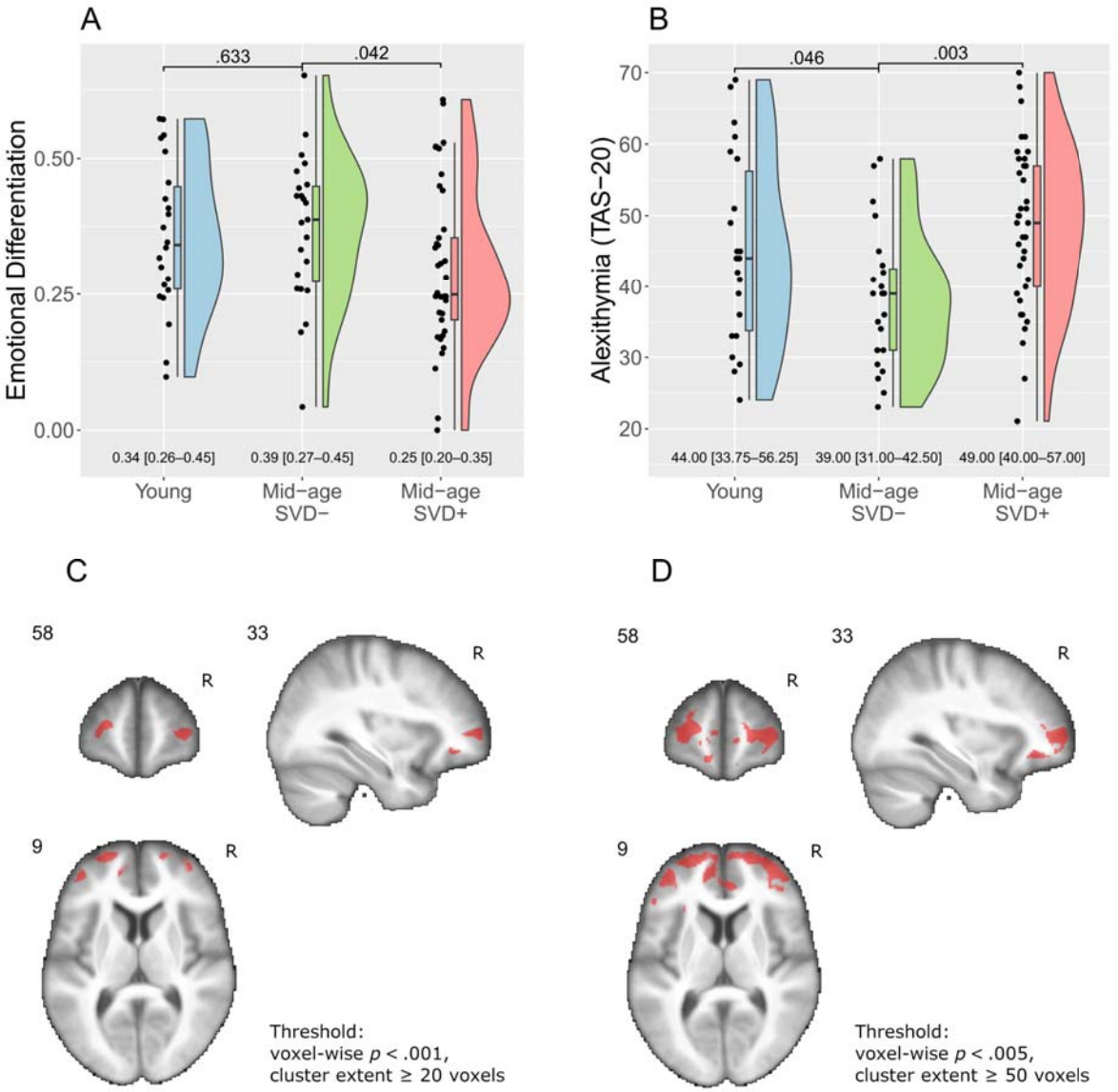

Figure 2. Emotional Differentiation in Healthy Ageing and Early Small Vessel Disease

Panels **A** and **B** indicate emotional differentiation measured in the social emotion fMRI task and the Toronto Alexithymia Scale (TAS-20) score in young adults, middle-aged adults without cerebral small vessel disease (mid-age SVD−), and middle-aged adults with SVD (mid-age SVD+). Median and [IQR] for each group are presented. On the raincloud plot, dots correspond to individual observations, bar plots represent the median and interquartile range, and data distribution is shown by the density plot. Significance is indicated for pairwise group comparisons, false discovery rate corrected. Panels **C** and **D** show the correlation between emotional differentiation and functional activation in the social emotion task, overlaid over the mean group anatomy (Emotion vs. Pixel contrast; emotional differentiation as a second-level covariate; N = 82). Fragmented activation in the prefrontal cortex is seen at voxel-wise $p < .001$, with no cluster-level significance (C). At voxel-wise $p < .005$, the distributed effect across bilateral prefrontal cortex forms a cluster of 16,408 mm^3, significant at the cluster-level p-FDR < .0001 (D).

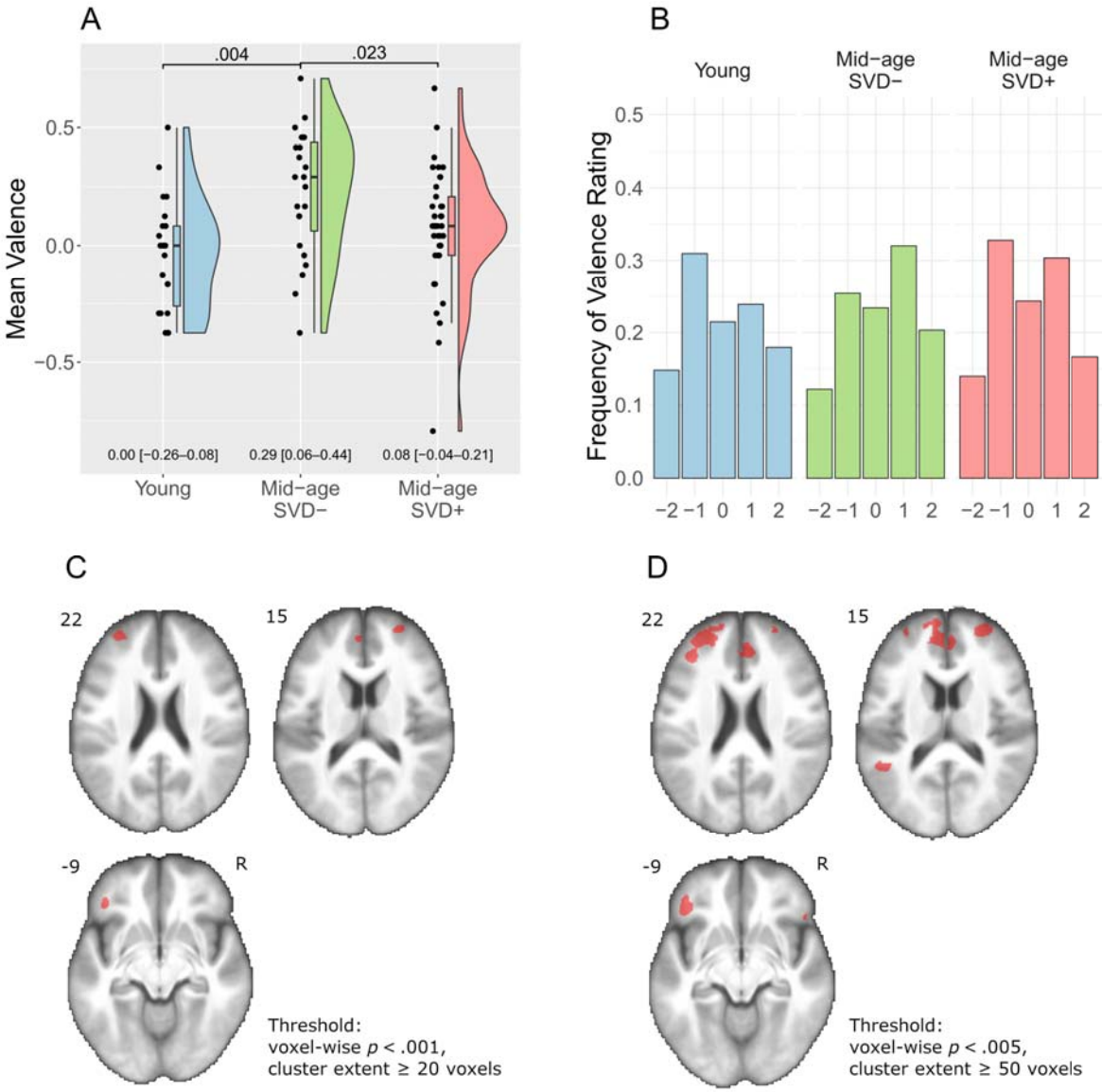

Figure 3. Positivity in Healthy Ageing and Early Small Vessel Disease

A. Mean valence rating in the social emotion fMRI task in young adults, middle-aged adults without cerebral small vessel disease (mid-age SVD−), and middle-aged adults with SVD (mid-age SVD+). Median and [IQR] for each group are presented. On the raincloud plot, dots correspond to individual observations, bar plots represent the median and interquartile range, and data distribution is shown by the density plot. Significance is indicated for pairwise group comparisons, false discovery rate corrected. **B**. Frequency with which participants from the three groups used valence ratings ranging from −2 (negative emotion) to +2 (positive emotion). Panels **C** and **D** show the correlation between mean valence and functional activation in the social emotion task, overlaid over the mean group anatomy (Emotion vs. Pixel contrast; mean valence as a second-level covariate; N = 82). The fragmented effect in the prefrontal cortex did not reach the cluster-level significance.

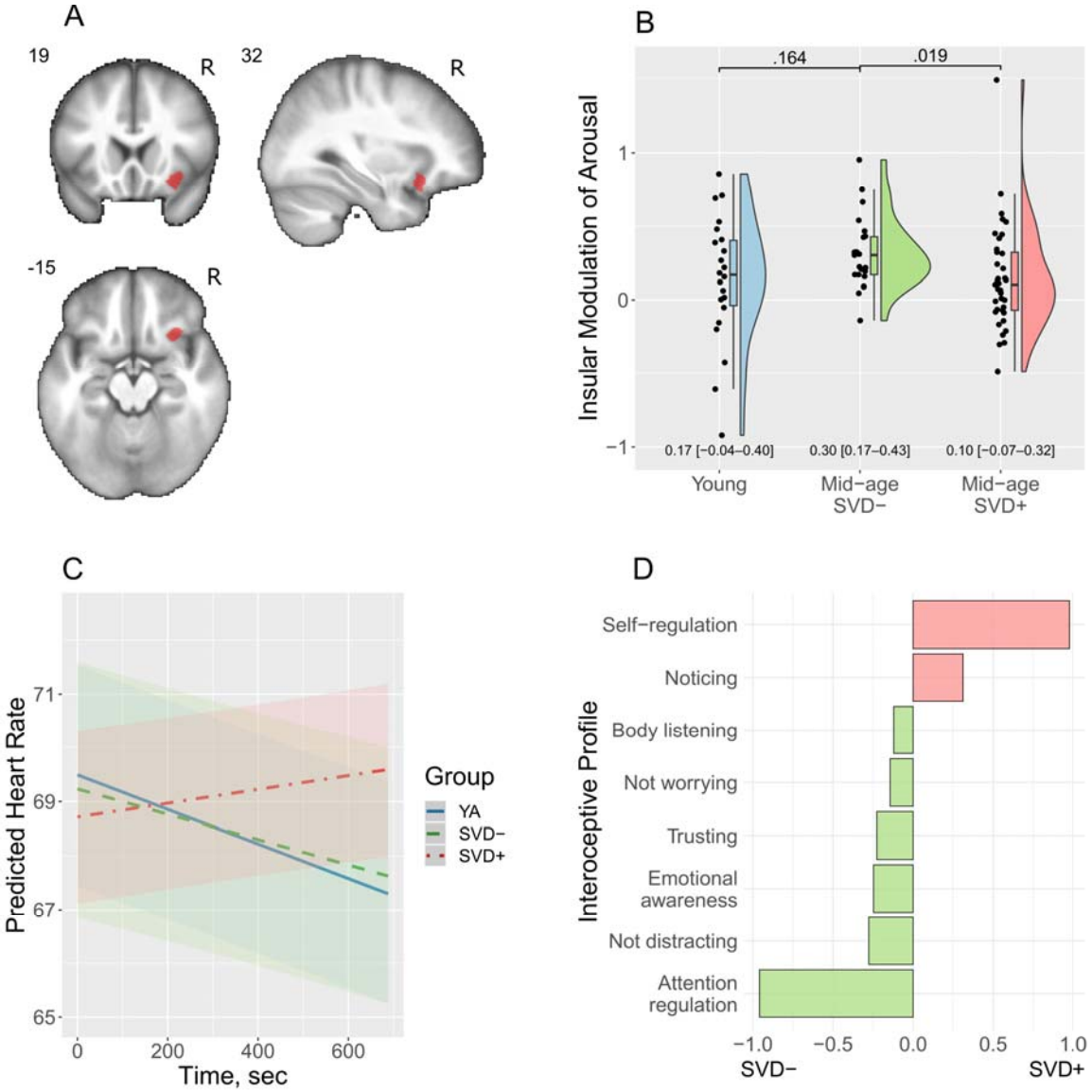

Figure 4. Neurovisceral Integration in Healthy Ageing and Early Small Vessel Disease

A. Region of interest (ROI) in the right ventral anterior insula, overlaid on the group-averaged anatomical image. **B.** Strength of BOLD signal modulation by arousal ratings within the ROI, estimated from first-level analyses using arousal as a parametric modulator in young adults, middle-aged adults without cerebral small vessel disease (mid-age SVD−), and middle-aged adults with SVD (mid-age SVD+). Median and [IQR] for each group are presented. On the raincloud plot, dots correspond to individual observations, bar plots represent the median and interquartile range, and data distribution is shown by the density plot. Significance is indicated for pairwise group comparisons, false discovery rate corrected. **C**. Predicted heart rate dynamics during the task in young adults (YA), middle-aged adults without cerebral small vessel disease (SVD−), and middle-aged adults with SVD (SVD+), estimated from a linear mixed-effects model with time-by-group interaction. Shaded areas indicate standard error. **D**. Contribution of interoceptive self-report subscales of the Multidimensional Assessment of Interoceptive Awareness (MAIA-2) to the discriminant function distinguishing middle-aged adults with and without SVD. Positive values indicate higher reported levels in SVD+ compared to SVD−. Subscales are ordered by loading magnitude. Colour indicates the direction of association (pink for higher in SVD+, green for higher in SVD−), and labels on the x-axis summarise each MAIA-2 subscale.

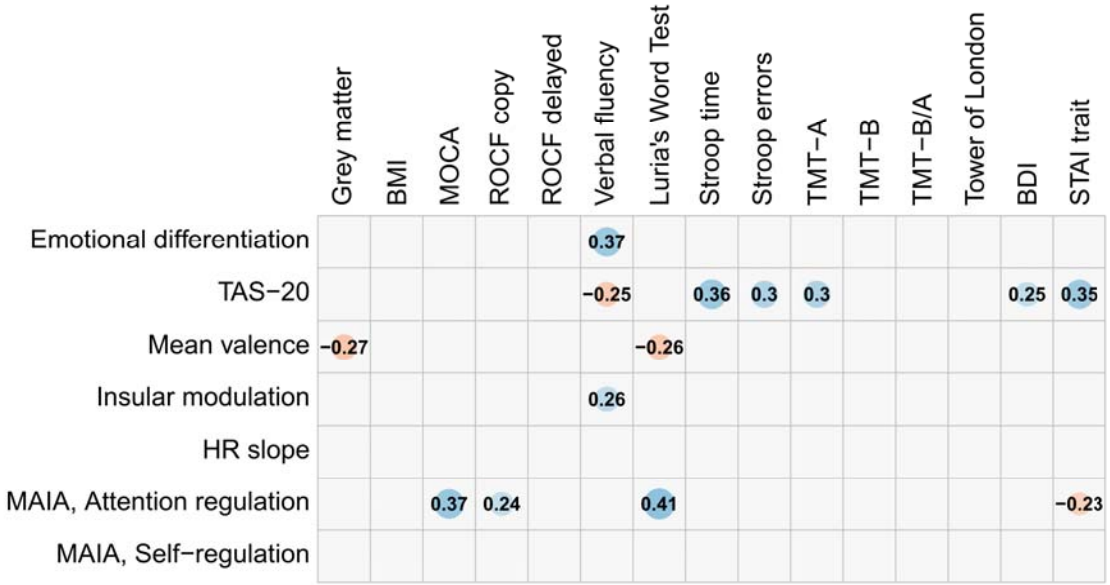

Figure 5. Role of Structural, Cognitive, and Affective Factors in the Effects of Interest

Spearman correlation coefficients are shown between variables of interest and candidate confounders. Note that Luria's Memory Word Test, Verbal Fluency, Stroop, Trail Making Test (TMT), and Tower of London tests were performed only in middle-aged adults. Only statistically significant associations ($p < .05$) are displayed; correlation coefficients are annotated numerically.