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Fluoxetine and brain connectivity after ischaemic stroke (RECONISE): a randomised controlled trial

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Abstract

Ischaemic strokes frequently lead to persistent motor deficits. Fluoxetine has been reported to enhance cerebral plasticity and neurogenesis. However, its impact on post-stroke recovery remains debated. Its influence on the reorganisation of brain connectivity has not yet been investigated. We therefore examined whether fluoxetine modifies the evolution of resting-state functional connectivity in patients with stroke-related motor deficits.

We conducted a randomised, placebo-controlled, double-blind trial, including patients aged 18-85 years who had experienced a stroke within the previous 10 days and had an NIHSS score > 8 and/or an NIHSS motor score > 4. Twenty-four patients were randomly assigned to fluoxetine (20 mg per day, *n* = 12) or placebo (*n* = 12) for 90 days. The primary outcome was the change in resting-state functional connectivity between baseline and day 90.

Seventeen patients were included in the analysis (fluoxetine n=8; placebo n=9). Resting-state functional connectivity decreased significantly in the fluoxetine group compared with the placebo (TFCE = 353.87, *P-FWE* = 0.001). This change was localised to a cluster involving the bilateral motor system, including the precentral gyrus, postcentral gyrus, juxtapositional lobule cortex, and superior parietal lobules. Interhemispheric connections represented 70.6% of this cluster. DTI suggested better preservation of corpus callosum integrity in the fluoxetine group.

In patients with stroke-related motor deficits, fluoxetine targeted the sensory-motor network and influenced inter-hemispheric connectivity. These findings reignite the debate over whether fluoxetine might influence motor recovery in patients with severe motor impairments and, in any case, should be considered in functional connectivity studies of stroke.

Introduction

More than seven million people worldwide experience ischaemic stroke (IS) each year,[1] and its burden in Europe is expected to increase in the coming years.[2] Many survivors remain chronically disabled, with 40% experiencing severe disability.[3] Among these impairments, upper limb paresis is a major contributor to long-term functional limitation.[4] Several pharmacological agents have been investigated for their potential to improve the functional outcomes in such patients. In 2011, the FLAME trial demonstrated the benefits of fluoxetine, a selective serotonin reuptake inhibitor (SSRI), in enhancing motor recovery following an IS with motor deficits.[5] More recent studies have also reported improvements in motor recovery with SSRIs.[6-8]

However, this effect was not confirmed in three subsequent large-scale studies (FOCUS, AFFINITY and EFFECT) which assessed a six-month treatment duration.[9-11] These trials, notably, used a different dosage and included a heterogeneous population comprising both ischaemic and haemorrhagic strokes, variable neurological impairments, and no systematic motor deficits. This methodological variability is particularly relevant, as stroke type (ischaemic or haemorrhagic) and initial motor severity are

established determinants of functional prognosis and recovery potential.[3,12] Moreover, large-scale trials cannot feasibly include long but sensitive measures such as the Fugl-Meyer scale, the gold standard for assessing sensorimotor recovery. Fluoxetine remains of considerable interest in the treatment of IS. However, its target population has yet to be clearly defined. Its use may be particularly relevant in patients with IS who present with severe motor impairments.

The mechanisms underlying motor system reorganisation following IS have become increasingly well characterised. Cerebral infarction induces spontaneous structural remodelling, involving both perilesional regions and the contralesional hemisphere.[13] This process induces a functional reorganisation of the brain, resulting in modifications of the connectome and evolving activity in regions remote from the focal lesion.[14] Clinical sequelae therefore reflect dysfunctions within cerebral networks, including areas not directly affected by the infarct. Recent advances in neuroimaging have demonstrated that these networks can be characterised through resting-state functional connectivity (rsFC) mapping.[15-17] Its post-stroke evolution and its association with deficit recovery have now been characterised.[18,19] Functional connectivity after stroke is a dynamic process that extends beyond the sensorimotor network, particularly in the acute stage, but tends to re-engage this network in case of favourable recovery. Accordingly, rsFC is considered a potential biomarker of post-stroke brain function and recovery capacity.[20]

Through their effect on intracortical inhibition and cortical excitability, SSRIs have been shown to promote a reactivation of a critical period of cerebral plasticity.[21,22] In animal models, fluoxetine has also been shown to reduce lesion volume and favourably modulate post-stroke cellular regeneration.[23] It may therefore enhance both structural and functional brain remodelling following stroke. In patients with major depressive disorder, SSRIs have been shown to reduce rsFC across several brain networks.[24] However, this mechanism does not appear to account for the effect of fluoxetine observed after IS. Indeed, Pariente et al. reported that a single dose of fluoxetine administered to stroke patients increase activation of the ipsilesional primary motor cortex during a motor task involving the injured limb.[25] Evaluating the effect of fluoxetine on the evolution of rsFC following IS is therefore essential to better understand its mechanisms of action, yet this has not previously been investigated.

In this study, we aimed to investigate the effect of fluoxetine on changes in rsFC over the 90 days following IS. We hypothesised that fluoxetine modulates the spontaneous functional reorganisation observed after a stroke, potentially contributing to improved functional outcomes. Given its broad effects on functional brain networks in healthy individuals,[26] we conducted a whole-brain connectivity analysis, rather than focusing solely on motor-related networks. To further explore the structural mechanisms underlying these changes, we complemented our analysis with diffusion tensor imaging (DTI).

Materials and Methods

Study design

The RECONISE study was a prospective, randomised, double-blind, placebo-controlled trial conducted between May 2017 and January 2022 in Department of neurology at Toulouse University Hospital.

Participants were randomly assigned to receive either fluoxetine (20 mg per day, orally) or placebo for 90 days. Study visits were scheduled at baseline, day 30, and day 90. At each visit, patients underwent clinical examination, and concomitant treatments were recorded. Neurological status was assessed using the National Institutes of Health Stroke Scale (NIHSS) and the modified Rankin scale (mRS). Adverse events and treatment adherence were monitored at day 30 and day 90. Structural and functional brain MRI were acquired at baseline and day 90. The primary outcome was the change in rsFC baseline and day 90. Secondary endpoints included NIHSS and mRS assessed at baseline, day 30, and day 90, as well as structural change in white matter within the motor network, evaluated using DTI.

The study was conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines. Ethical approval was obtained from the independent local ethics committee (Comité de protection des personnes Sud-Ouest et Outre Mer III), and written informed consent was provided by all participants. It was registered on 6 May 2016 at ClinicalTrials.gov (NCT02767999).

Randomisation and masking

Randomisation was performed in a 1:1 ratio using a random block allocation sequence generated by the study biostatistician. Participants were assigned to one of the two treatment arms by the pharmacist, based on the randomisation list. Fluoxetine and placebo were prepared in identical packaging, labelling, and presentation to ensure blinding. The treatment was then delivered to the medical department labelled only with the patient's identification number. The Clinical Investigation Centre (Toulouse, France), an independent body, was responsible for study coordination. All participants, clinical staff, investigators, and statisticians remained blinded to treatment allocation throughout the study.

Population

Patients were eligible if they had experienced a first cortical or subcortical IS within the previous 10 days, confirmed by brain MRI. Inclusion criteria were: age between 18 and 85 years, a minimum NIHSS score of 8 and/or a minimum motor NIHSS of 4 on the affected limb, and affiliation with a public healthcare system. Exclusion criteria included: NIHSS ≥ 22, a history of treated depressive disorder, chronic alcoholism, hepatic or renal failure, current or recently discontinued (within the past 6 weeks) SSRI treatment, pregnancy, severe language or comprehension deficits, and contraindications to either MRI or fluoxetine.

MRI acquisition

MRI data were acquired at the INSERM ToNIC laboratory (Toulouse NeuroImaging Centre), located within the University Hospital of Toulouse (France), using a 3.0 Tesla Philips scanner equipped with a 32-channel head coil and echo-planar sequence imaging (EPI) technology. All participants underwent structural MRI, including a high-resolution 3D T1-weighted MP-RAGE sequence (repetition time [TR] = 8.1 ms, echo time [TE] = 3.7 ms, flip angle = 8°, voxel size = 1.0 x 1.0 x 1.0 mm), and a T2-weighted FLAIR sequence (fluid-attenuated inversion recovery, repetition time = 8000 ms, echo time = 343 ms, flip angle = 90°, voxel size = 1.0 x 1.0 x 1.0 mm). Resting-state functional MRI was acquired with the following parameters: TR = 2500 ms, TE = 30 ms, flip angle = 90°, voxel size = 3.0 x 3.0 x 3.0 mm, 46 transversal slices. During acquisition, participants were instructed to fixate on a white cross displayed on a black screen while remaining at rest. DTI was also acquired (TR = 8200 ms, TE = 75 ms, flip angle = 90°, voxel size = 2 x 2 x 2 mm).

Resting state functional MRI

Resting-state functional connectivity (rsFC) analyses were performed using CONN toolbox[27] (version 20.b;RRID:SCR_009550) and SPM (RRID:SCR_007037; release 12.7771). In nine participants, lesions were located in the right hemisphere. To enable consistent group level analyses, all structural and functional MRI images were rotated 180° in sagittal plane, such that lesions were consistently lateralised to the left hemisphere. This approach is recommended for harmonising data from patients with lesions in different hemispheres.[28] The description of the preprocessing, denoising, and first- and second-level analysis steps provided below is based on the CONN toolbox report.

Preprocessing

Functional and anatomical data were preprocessed using a flexible preprocessing pipeline[29] including realignment with correction of susceptibility distortion interactions, slice timing correction, outlier detection, direct segmentation, and MNI-space normalization, and smoothing. Functional data were realigned using SPM realign & unwarp procedure,[30] where all scans were coregistered to a reference image (first scan of the first session) using a least squares approach and a 6 parameter (rigid body) transformation, and resampled using b-spline interpolation to correct for motion and magnetic susceptibility interactions. Temporal misalignment between different slices of the functional data (acquired in interleaved bottom-up order) was corrected following SPM slice-timing correction (STC) procedure,[31] using sinc temporal interpolation to resample each slice BOLD timeseries to a common mid-acquisition time. Potential outlier scans were identified using ART as acquisitions with framewise displacement above 0.9 mm or global BOLD signal changes above 5 standard deviations, and a reference BOLD image was computed for each subject by averaging all scans excluding outliers. Functional and anatomical data were normalized into standard MNI space, segmented into grey matter, white matter, and CSF tissue classes, and resampled to 3 mm isotropic voxels following a direct normalization procedure[32] using SPM unified segmentation and normalization algorithm[33,34] with

the default IXI-549 tissue probability map template. Last, functional data were smoothed using spatial convolution with a Gaussian kernel of 7 mm full width half maximum (FWHM).

Denoising

In addition, functional data were denoised using a standard denoising pipeline[29] including the regression of potential confounding effects characterized by white matter timeseries (5 CompCor noise components), CSF timeseries (5 CompCor noise components), PPU regressors (6 components), motion parameters and their first order derivatives (12 factors),[35] outlier scans (below 91 factors), session and task effects and their first order derivatives (4 factors), and linear trends (2 factors) within each functional run, followed by bandpass frequency filtering of the BOLD timeseries[36] between 0.008 Hz and 0.09 Hz. CompCor[37,38] noise components within white matter and CSF were estimated by computing the average BOLD signal as well as the largest principal components orthogonal to the BOLD average, motion parameters, and outlier scans within each subject's eroded segmentation masks.

First-level analysis

ROI-to-ROI connectivity (RRC) matrices were estimated characterizing the functional connectivity between each pair of regions among 132 Harvard-Oxford atlas ROIs[39]. Functional connectivity strength was represented by Fisher-transformed bivariate correlation coefficients from a general linear model (weighted-GLM),[29] estimated separately for each pair of ROIs, characterizing the association between their BOLD signal timeseries. Individual scans were weighted by a boxcar signal characterizing each individual task or experimental condition convolved with an SPM canonical hemodynamic response function and rectified.

Second-level analyses

Group-level analyses were performed using a General Linear Model (GLM).[29] For each individual connection a separate GLM was estimated, with first-level connectivity measures at this connection as dependent variables (one independent sample per subject and one measurement per task or experimental condition, if applicable), and groups or other subject-level identifiers as independent variables. Connection-level hypotheses were evaluated using multivariate parametric statistics with random-effects across subjects and sample covariance estimation across multiple measurements. Inferences were performed at the level of individual clusters (groups of contiguous connections). Cluster-level inferences were based on nonparametric statistics using Threshold Free Cluster Enhancement (TFCE),[40] with 1000 residual-randomization iterations, and ROIs sorted using optimal leaf ordering based on ROI-to-ROI anatomical proximity and functional similarity metrics.[29,41] Results were thresholded using a familywise corrected *P-FWE* < 0.05 TFCE-score threshold.

DTI

Diffusion-weighted images were processed using Diffusion Spectrum Imaging (DSI) Studio software (http://dsi-studio.labsolver.org). All datasets were corrected for eddy currents and head motion. With white matter Human Connectome Project atlas (HCP842 atlas), fiber tracking was based on an automatic fiber tracking function and a deterministic fiber tracking algorithm using a track recognition based on the tractography atlas.[42] Normalized diffusion images were superimposed on the MNI template for each subject to check normalization. Voxels with zero intensity were automatically excluded. The fractional anisotropy (FA) threshold was set to 0.2, and the angular threshold ranged between 45 and 65°. DTI metrics were extracted from regions of interest (ROI) defined by the Johns Hopkins University atlas.

Lesion segmentation

Ischemic brain lesions were manually segmented using ITK-SNAP software[43], based on T2-weighted FLAIR sequences previously normalised to the Montreal Neurological Institute (MNI) brain template. The resulting lesion masks were used to quantify lesion volume and were subsequently compiled using MRIcron[44] software to generate lesion overlap maps. These masks were also employed to compute corticospinal tract (CST) involvement. For each patient, the number of voxel overlapping both the lesion and the CST was calculated, using CST regions derived from the John Hopkins University (JHU) white matter atlas,[45-47] including the posterior limb of the internal capsule, superior corona radiata, cerebral peduncle, as well as the pontine and bulbar CST segments.

Statistical analysis

When the protocol was developed, no sufficiently detailed data were available on changes in cerebral connectivity assessed with resting-state fMRI to allow for an accurate estimation of fluoxetine's effect on this parameter. The study was initially planned to take place in two French centres and to include a total of 60 patients. However, due to logistical constraints and the subsequent COVID-19 pandemic, it was ultimately conducted at a single centre. The target sample size was therefore revised. Given the exploratory nature of our study and in line with other recent investigations of rsFC following stroke[20,48,49], we aimed to include 20 patients (10 per group). Due to the small sample size, non-parametric tests were employed for statistical analyses of clinical data. Between-group comparisons at each time point were conducted using the Mann-Whitney U test. Within-group changes in clinical scores across time points were assessed using the Kruskal-Wallis test, followed by pairwise comparisons using the Wilcoxon signed-rank test, with Holm's method applied for multiple comparisons correction. A two-tailed $P < 0.05$ was considered statistically significant.

Between-group comparisons of rsFC at days 0 and day 90 were performed using two-sample t-test. Within-group longitudinal changes in rsFC were assessed using paired t-test. To compare rsFC changes over time between groups, a two-way mixed analysis of variance (ANOVA) was conducted, adjusted for age and lesion volume. Statistical significance was defined as *P-FWE* < 0.05. The false discovery rate

(FDR) approach was also performed. To analyse DTI changes, individual delta values (day 90 – day 0) were calculated for each parameter. Between-group comparisons of these deltas were performed using Mann–Whitney U tests, with two-tailed *P-value* < 0.05 considered statistically significant.

Clinical and DTI data were analysed using RStudio software,[50] which was used for both statistical computations and graphical visualisations. Imaging analyses were conducted using the CONN functional connectivity toolbox.

Results

Population

Between May 2017 and January 2022, 27 patients were prospectively enrolled. Three were excluded prior to randomisation, including one who showed clinical improvement and no longer met the inclusion criteria (Fig. 1). The remaining 24 patients were randomised and allocated evenly between the fluoxetine and placebo groups (*n* = 12 per group).

Among those randomised, five participants did not complete the day-90 MRI scan: three due to the COVID-19 pandemic, one who withdrew consent, and one who died before day 90 (Fig. 1). Two additional patients were excluded from the final analysis: one due to missing MRI data (panic attack during acquisition), and one who received fluoxetine during rehabilitation, violating the study protocol. The primary endpoint was therefore analysed in 17 patients: eight in the fluoxetine group and nine in the placebo group.

The two groups were comparable in terms of demographic characteristics and initial stroke treatment, except for age, which was higher in the placebo group (Table 1). In this group, both the percentage of corticospinal tract involvement and lesion volume were also greater (Table 1). Nevertheless, baseline NIHSS and mRS were similar between groups.

Most patients had a lesion involving the middle cerebral artery territory and the internal capsule (Fig. 2). Three patients (two in the fluoxetine group and one in the placebo group) had brain stem lesions (Fig. 2).

Resting state FC evolution

To address the primary endpoint, changes in rsFC over the 90-day study period were compared between the two groups. Because age differed between groups, additional analyses were performed to assess its potential influence on rsFC changes. Age was included as a covariate in the second-level analysis. In addition, the individual change in rsFC (DeltaFC = $FC_{Day90} - FC_{Day0}$) extracted from the cluster reported below was examined in relation to age. No significant correlation between age and DeltaFC was observed (r = 0.19, *P-value* = 0.46; Supplementary Fig. 1). These results suggest that the observed group

difference in rsFC change was not driven by age differences between groups. Because lesion volume also differed between groups, it was similarly included as a covariate in the second-level analysis.

The fluoxetine group exhibited a significant reduction in rsFC compared with the placebo group, with a cluster of decreased functional connectivity (TFCE = 353.87, *P-unc* < 0.0001, *P-FDR* = 0.002, *P-FWE* = 0.001) (Fig. 3). This connectivity cluster corresponded to the bilateral motor system and included the primary and secondary motor cortices (specifically the precentral gyrus (PreCG), postcentral gyrus (PostCG), and juxtapositional lobule cortex (SMA)) in both damaged and undamaged hemispheres, as well as the bilateral superior parietal lobules (SPL) (Fig. 3A). Within this cluster, 70.6% of the connections were interhemispheric (12 out of 17), 17.6% were intrahemispheric within the undamaged hemisphere (3 out for 17), and 11.8% were intrahemispheric within the damaged hemisphere (2 out for 17) (Fig. 3B). Mean rsFC values for the identified cluster at day 0 and day 90 for each group are shown in Figure 3.C. No significant differences in rsFC were observed between the fluoxetine and placebo groups, either at baseline (Day 0) or at Day 90. Similarly, no within-group changes in rsFC were statistically significant over the 90-day period. Detailed rsFC values for each connection within the identified cluster are provided in the supplementary material (Supplementary Fig. 2).

Clinical outcomes

Both the fluoxetine and placebo groups demonstrated significant improvement in NIHSS scores over the 90-day follow-up period (Fig. 4). In the fluoxetine group, the median NIHSS score decreased from 12.5 [11.0;16.0] at baseline to 8.00 [6.75;10.75] at Day 30 (*P-unc* = 0.01, *P-corr* = 0.04), and to 5.50 [5.00;7.50] at Day 90 (baseline vs Day 90: *P-unc* = 0.01, *P-corr* = 0.04; Day 30 vs Day 90: *P-unc* = 0.23, *P-corr* = 0.23).

In the placebo group, the median NIHSS score declined from 14.0 [12.0;15.0] at baseline to 9.0 [8.0;10.0] at Day 30 (*P-unc* = 0.01, *P-corr* = 0.03), and to 5.0 [4.0;8.0] at Day 90 (baseline vs Day 90: *P-unc* = 0.01, *P-corr* = 0.03; Day 30 vs Day 90: *P-unc* = 0.01, *P-corr* = 0.03). At no time point (baseline, Day 30, or Day 90), did NIHSS scores differ significantly between groups. The mRS score, reflecting functional independence, also improved in both groups over the study period, with no significant between-group differences at any time point (Fig. 5).

Among the 24 patients receiving study treatments, a total of 47 adverse events were reported (Supplementary Table 1). The three most frequent events were infection (3 [13.6%] in the fluoxetine group vs 7 [28.0%] in the placebo group), constipation (4 [18.2%] vs 5 [20.0%]), and psychiatric disorders (2 [9.1%] vs 5 [20.0%]). Notably, cytopenia and bone fractures occurred exclusively in the fluoxetine group. No serious treatment-related adverse events were reported during the study.

DTI

To investigate structural changes in white matter over the 90-day period, motor-related networks were analysed using DTI. In the fluoxetine group, a significant improvement in the microstructure of the body of the corpus callosum in the damaged hemisphere was observed compared with the placebo group (Supplementary Fig. 3). This was reflected by a smaller increase in the damaged/undamaged (D/U) ratio of the mean diffusivity (MD_r) and radio diffusivity (RD_r) parameters (median MD_r change: 0.02 [0.01;0.02] vs 0.09 [0.05;0.15], P = 0.030; median RD_r change: 0.02 [-0.01;0.03] vs 0.15 [0.07;0.18], P = 0.045). In fluoxetine group (n=5), there was also a significantly greater increase in the D/U ratio of the axial diffusivity (AD_r) parameter in the corticospinal tract compared with the placebo group (n=8, median AD_r change: 0.20 [0.07;0.21] vs 0.04 [0.00;0.10], P = 0.045). No significant between-group differences were observed for the other DTI parameters (Supplementary Fig. 3).

However, the increase in the RD_r within the medulla was significantly greater in the fluoxetine group, potentially indicating reduced microstructural integrity at day 90 (median RD_r change: 0.12 [0.11;0.15] vs 0.07 [0.01;0.11], P = 0.045) (Supplementary Fig. 3). No significant between-group differences were observed for the other medulla parameters. Similarly, no significant differences in evolution were detected for any of the remaining white matter ROIs (Supplementary Fig. 3).

Discussion

In this study, we examined the effect of a 90-day fluoxetine treatment on rsFC to elucidate its role in intracerebral reorganisation during post-stroke recovery. Fluoxetine was associated with a significant reduction in rsFC between regions of the bilateral motor system. Over the same period, DTI analyses suggested that fluoxetine administration attenuated microstructural damage to the corpus callosum.

Fluoxetine-associated changes in functional connectivity following stroke

The effects of SSRIs on rsFC have been extensively investigated in the context of major depressive disorder. In this setting, SSRI treatment appears to restore disordered connectivity patterns,[51] particularly within the default mode network (DMN), with rsFC either increasing or decreasing depending on the specific DMN subcomponent involved.[52] Twelve weeks of SSRI administration have been shown to increase rsFC between subcortical networks and the ventral attention networks, connectivity that is initially reduced in major depressive disorder and subsequently normalises towards healthy-control levels in parallel with clinical improvement.[53]

Conversely, SSRIs have been reported to reduce rsFC within the thalamo-cortico-periaqueductal network, which is implicated in pain processing.[54] In healthy individuals, SSRI decrease rsFC within DMN and in the task-positive network (intraparietal sulcus-occipital gyrus connection), a circuit generally recruited during goal-directed behaviour.[55] These findings indicate that fluoxetine can modulate functional connectivity in distinct brain networks, with effects varying according to whether baseline connectivity is reduced or increased.

In this study, we report, to our knowledge for the first time, the effects of fluoxetine on post-stroke rsFC evolution in patients with motor deficits. Fluoxetine did not modulate rsFC within the previously described networks but it exerted a significant influence on the bilateral sensorimotor network (SMN). In line with previous reports, IS initially causes a reduction in cerebral connectivity, followed by a spontaneous evolution marked by increased interhemispheric rsFC, most notably between ipsilesional motor areas and contralesional regions such as the SPL, anterior intraparietal sulcus or SMA.[14,56,57] In contrast, our findings indicate that fluoxetine treatment, administered over 90 days post-stroke, was associated with a reduction in sensorimotor rsFC, predominantly across interhemispheric connections, and including the contralesional SPL and the SMA. These results suggest that fluoxetine may modulate distinct brain networks, with its effects potentially determined by the underlying pathology and baseline rsFC alterations.

In animal models of stroke, SSRI administration initially reduces inhibitory tone in perilesional tissue, which in turn facilitates the recruitment of new connections. This process helps restore the inhibition-excitation balance between the ipsilesional and contralesional hemispheres, ultimately enabling the re-establishment of effective circuits within the ipsilesional hemisphere.[21] This effect may be linked to SSRI-induced increases in BDNF levels in perilesional regions, which promote neurogenesis and neoangiogenesis around infarcted areas.[58] More recently, fluoxetine has been shown to reduce the production of circular RNAs,[23] biomarkers implicated in inflammation and cell survival during stroke.[59] More specifically, in animal stroke models, fluoxetine has been shown to promote the regeneration of serotonergic and noradrenergic perilesional innervation.[60] Recent evidence indicates that brain chemoarchitecture, closely correlated with functional connectivity, links motor regions and interhemispheric pathways via serotonergic and noradrenergic neurotransmission.[61,62] This could account for the targeted effect of fluoxetine on bilateral motor regions observed in our study. However, in our cohort, fluoxetine was associated with a decrease in functional connectivity, suggesting a more complex mechanism. Fluoxetine can modulate synaptic transmission through both excitatory and inhibitory effects, and in our case, the reduction in connectivity may also reflect inhibitory potentiation mediated by the GABAergic system.[63] Taken together, these findings indicate that fluoxetine may exert targeted effects on brain regions impacted by stroke, particularly within the sensorimotor system. This may account for our observation that fluoxetine influenced sensorimotor connectivity in a manner distinct from the patterns typically reported in major depressive disorder. Our data therefore reinforce the view that fluoxetine has stroke-specific actions that extend beyond its established role in treating post-stroke depression, as proposed in earlier studies.[64,65]

Finally, the effect of fluoxetine-related changes in rsFC observed in our study is similar to that reported with other post-stroke interventions. For instance, motor imagery therapy and robot-assisted rehabilitation have been shown to decrease interhemispheric functional connectivity between sensorimotor cortices.[66,67] Similarly, administration of modafinil has been associated with reduced FC within the sensorimotor network and with a significant improvement in post-stroke fatigue.[48]

Impact of reduced interhemispheric functional connectivity after stroke

Our findings indicate that fluoxetine was associated with a reduction in rsFC within the bilateral SMN, particularly between the pre-CG, post-CG, SMA, and SPL. This reduction predominantly involved interhemispheric connections, accounting for 70.6% of the identified links.

Following an initial decrease in interhemispheric rsFC during the acute phase, several studies have reported a spontaneous increase in interhemispheric connectivity in stroke patients compared with healthy controls.[56,57] This increase is often accompanied by an asymmetry of primary motor cortex (M1) connectivity, favouring the contralesional hemisphere.[57] Such abnormal enhancement reflects a reorganisation of brain activity in intact regions to compensate for areas with similar functions damaged by the stroke.[14,68] Notably, specific interhemispheric connections have been associated with a more favourable functional prognosis, including connectivity between the ipsilesional M1 and contralesional SMA,[57] as well as connectivity involving the contralesional SPL.[56]

Nevertheless, persistent increases in interhemispheric connectivity may reflect the enduring compensatory mechanism, potentially arising from irreversible connectivity damage within the ipsilesional hemisphere. Such compensation could reflect maladaptive plasticity, hindering optimal recovery through the affected hemisphere.[69] Consistent with this, persistent activation of contralateral motor regions during movement of the paretic limb has been shown to enhance interhemispheric inhibition from the healthy to the injured hemisphere, a phenomenon associated with poorer motor recovery.[68,70] Similarly, recent evidence suggests that increased functional connectivity within the healthy hemisphere correlates with greater residual deficits.[71] An increase in functional connectivity within the ipsilesional sensorimotor network, particularly between M1 and the premotor region, has also been associated with better subsequent recovery.[19,20] Park et al.[57] further reported that motor recovery was accompanied by a secondary increase in ipsilesional functional connectivity, evident as early as three months post-stroke, approaching levels observed in healthy individuals. Taken together, these findings suggest that restoring ipsilesional activity through reduced interhemispheric connectivity may be central to achieving better long-term motor recovery.

In our study, three months of fluoxetine treatment were associated with a reduction in interhemispheric rsFC, suggesting reduced involvement of the healthy hemisphere in organising the SMN. This pattern may reflect restoration of the interhemispheric inhibition-excitation balance, a mechanism previously attributed to fluoxetine in animal models.[21] This interpretation is further supported by our earlier findings showing that a single dose of fluoxetine in stroke patients was associated with increased activation of the primary motor cortex during active movement of the affected limb.[25] The results of our study may help explain why several previous reports have found fluoxetine to enhance motor recovery after stroke.[5-7] Nevertheless, the post-stroke evolution of functional connectivity remains incompletely understood with multiple, sometimes competing, theories, particularly concerning the role and consequences of interhemispheric connectivity. One possibility is that the evolution of SMN connectivity varies according to the patient's initial stroke severity and the specific structures initially affected.[72]

Our study population was initially homogeneous regarding the neurological consequences of stroke, with all participants meeting the inclusion criterion of severe neurological impairment and motor deficits. Over the course of the study, all patients demonstrated clinical neurological improvement (as measured by NIHSS) and gains in functional independence (as measured by mRS), with no significant differences between groups. This outcome is unsurprising given the sample sizes typically used in other clinical trials evaluating treatment efficacy.[5,9-11] Our study was not designed to assess the clinical efficacy of the treatment, and the sample size was therefore insufficient to determine whether the observed rsFC changes translate into clinical benefit. Nevertheless, Yu et al.[69] recently reviewed current evidence on post-stroke functional connectivity. Their analysis supports the view that early increase in interhemispheric connectivity may reflect diaschisis, serving to compensate for initial functional loss. Over time, however, subsequent reductions in interhemispheric connectivity, together with recovery of ipsilesional function, appear to be critical for achieving better long-term clinical outcomes.[69]

SMA and SPL connectivity in stroke recovery

While the preCG and postCG are the primary hubs of the SMN, responsible for voluntary motor execution and somatosensory processing, respectively, the SMA and SPL also play key roles.

Owing to its extensive connections with cortical and subcortical structures, including the primary motor cortex, the SMA supports the planning, coordination, and execution of complex motor actions.[73] The SPL integrates and processes sensory inputs—particularly visual and hand-related information—and contributes to the maintenance of working memory.[74]

In functional MRI studies of motor tasks in healthy individuals, the SMA and SPL are typically engaged during the execution of complex motor actions.[75] In stroke patients, however, these regions are recruited even for simple motor tasks.[76] Similar patterns have been reported in rsFC studies, showing increased interactions between the core motor network and networks involved in sensory perception as well as multimodal information integration.[77,78]

Stroke patients therefore appear to engage greater attentional resources than healthy individuals, likely due to the need to integrate and process a larger volume of sensory information to accomplish even simple tasks.[79] During the phase of secondary motor recovery, activation in these regions decreases,[76] reflecting the re-establishment of a functional motor network that no longer demands such extensive neural effort.

Brain activity at rest, as assessed for example through rsFC, entails substantial energy expenditure.[80] It is therefore plausible that the compensatory mechanisms and increased interactions described above impose an additional energetic cost. This may represent the cellular correlate of the heightened attentional demands observed in the early phase after stroke. In our study, fluoxetine was associated with reduced rsFC in bilateral SMA and SPL. Such a fluoxetine-induced reduction could reflect pharmacological modulation aimed at lowering resting-state energy consumption. This is also reminiscent of the results we had with chronic SSRI treatment where the decrease in fMRI activation in

healthy subjects was correlated with an improvement in motor performance (Loubinoux NeuroImage 2005).

Based on the literature, two interpretations of our findings are possible: (1) fluoxetine may directly limit the engagement of these regions in sensorimotor network reorganisation, thereby lowering brain energy demands; (2) in light of fluoxetine previously reported effects on interhemispheric connectivity, the observed reduction could instead indicate improved recovery of ipsilesional brain function.

DTI-based structural changes

DTI analysis revealed no deterioration in corpus callosum microstructure in the fluoxetine group, whereas the placebo group exhibited signs of progressive damage, evidenced by increases in MD and RD. Although interpretation is limited by the small sample size, these findings suggest that fluoxetine preserve the microstructural integrity of interhemispheric connections between sensorimotor cortical areas. Moreover, this supports the view that fluoxetine-induced changes in functional connectivity strength primarily reflect pharmacological modulation of neuronal function, rather than confounding effects of structural alterations.

Limitations

Although our study is, to our knowledge, the first to demonstrate the effect of fluoxetine on functional connectivity after stroke, it has several limitations. The sample size was admittedly small, which may have limited our ability to detect all possible effects of fluoxetine on rsFC changes in other brain regions. Nonetheless, the fact that we observed a clear and targeted pharmacological effect on the sensorimotor network suggests that this effect is robust. Previous work has shown that post-stroke changes in rsFC can also involve the cerebellum, occipital cortex, and insular regions, areas related to visual, sensory and salience information processing.[69] While we did not observe fluoxetine-related changes in these networks, our study may have been underpowered to detect them. It is therefore possible that fluoxetine could also enhance rsFC between regions where connectivity is initially reduced, as described in major depressive disorder.[53] The action of fluoxetine may thus be more complex than our findings alone suggest. Importantly, our analyses revealed a marked difference in rsFC evolution between groups, involving brain regions distinct from those typically reported in previous studies.

Secondly, the small sample size prevented us from assessing correlations between fluoxetine-induced rsFC changes and improvements in clinical scores. As a result, we cannot determine whether the observed connectivity changes translate into clinical benefit. Our primary aim, however, was to characterise fluoxetine's effects on rsFC rather than to test clinical efficacy. In achieving this aim, we provide mechanistic insights that may help resolve ongoing discrepancies in the literature regarding its role in post-stroke motor recovery. Nevertheless, DTI results suggest a beneficial effect of fluoxetine.

Another limitation is that some patients had brainstem lesions. While their clinical presentation may resemble that of middle cerebral artery strokes, the patterns of rsFC reorganisation could differ

substantially. In such cases, alterations may involve not only cortical functional connectivity but also cortico-subcortical networks.[81] Fluoxetine's effects might also differ in this subgroup. However, patients with subcortical lesions were evenly distributed across groups, and a sub-analysis excluding them yielded comparable results (data not shown). These findings suggest that brainstem lesions had no major influence on our conclusions.

Conclusion

Administration of fluoxetine for three months after ischaemic stroke with motor deficits was associated with reduced rsFC within the bilateral sensorimotor network, particularly between the PreCG, PostCG, SMA, and SPL. To our knowledge, this is the first report of fluoxetine effect on rsFC evolution after stroke. Further studies in patients with substantial motor impairment are warranted to clarify its clinical impact. Given its marked influence on functional connectivity, fluoxetine use could introduce bias in rsFC studies. Future research should account for this by stratifying patients according to treatment status.

Declarations

Competing interests:

PG has received speaker honoraria from Sanofi, with no conflict of interest with the work presented. **VF** has received travel grants from Abbott, Effik, Novartis, LFB, Sanofi, Alylam, Argenx, CSL Behring and honoraria for lectures from Argenx, with no conflict of interest with the work presented. **LC** has received honoraria from Bristol Myers Squibb and Pfizer, with no conflict of interest with the work presented. **JMO** has been a consultant for Boehringer and Roche, with no conflict of interest with the work presented. **The other authors** declare no known competing interests that could have influenced the work reported in this manuscript.

Author contribution

PG: experimental activity, clinical and imaging data analysis, made figures, article writing; MBG: conceptualization, experimental activity; VS: conceptualization, experimental activity; CT: conceptualization, study coordination; BB: conceptualization, clinical data analysis; NA: experimental activity, study coordination; VF: conceptualization, experimental activity; NR: conceptualization, experimental activity; LC: conceptualization, experimental activity; JFA: conceptualization, experimental activity; AV: conceptualization, experimental activity; LF: conceptualization, experimental activity; JMO: conceptualization, experimental activity; FC: conceptualization, study coordination; IL: conceptualization, experimental activity, study coordination, imaging data analysis, article writing.

All authors provided critical revision of the manuscript, participated in proofreading, and editing of the manuscript.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Ethics statement

RECONISE study was conducted in accordance with the principles of the Declaration of Helsinki and the good clinical practice guidelines. It has been approved by the local independent ethics committee, authorised by the French National Agency for the Safety of Medicines and Health Products (ANSM), and all participants provided written informed consent. It is registered on ClinicalTrials.org under number NCT02767999.

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Tables

Table 1 is available in the Supplementary Files section.

Figures

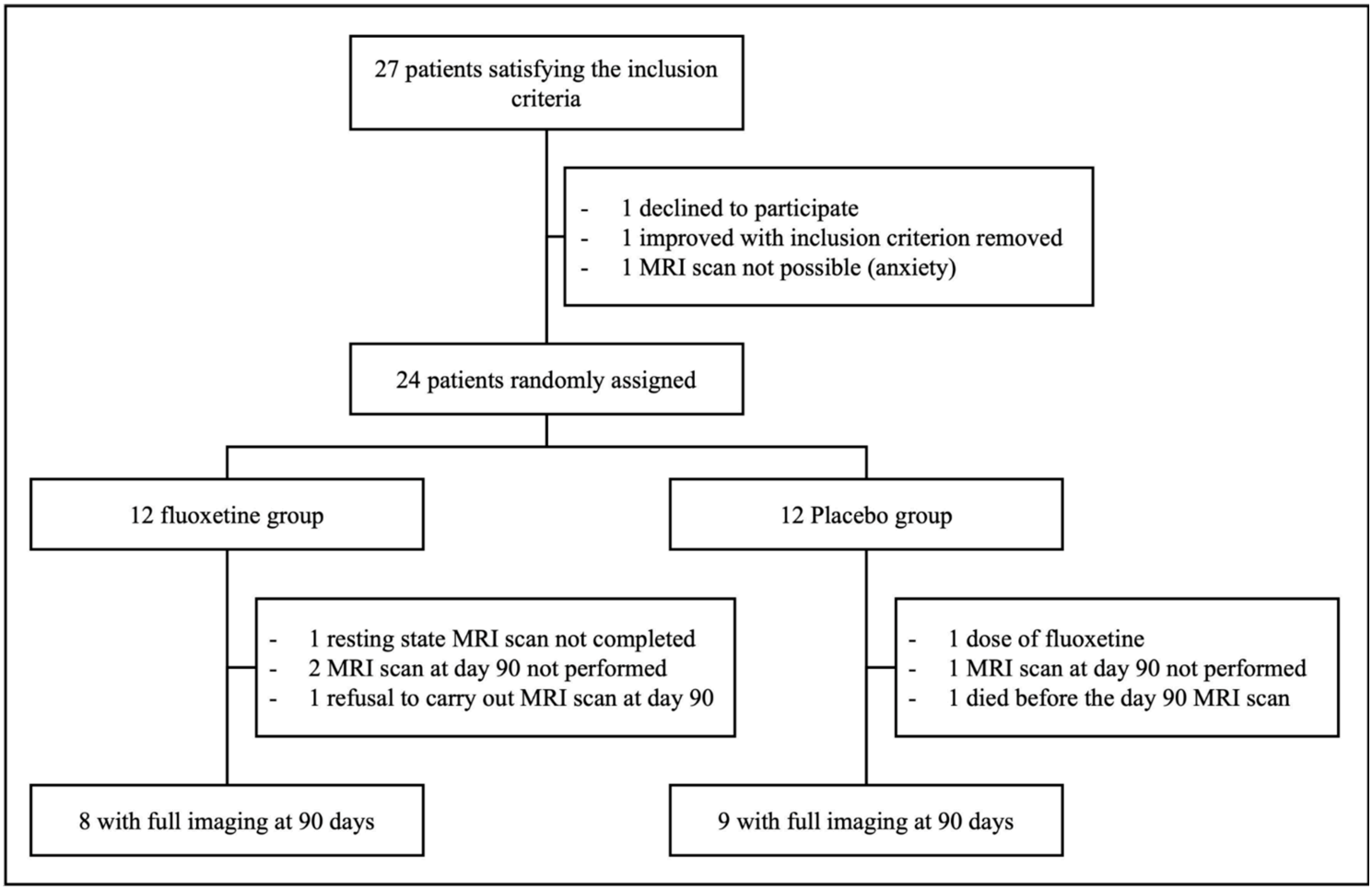


Figure 1

CONSORT diagram of patient recruitment

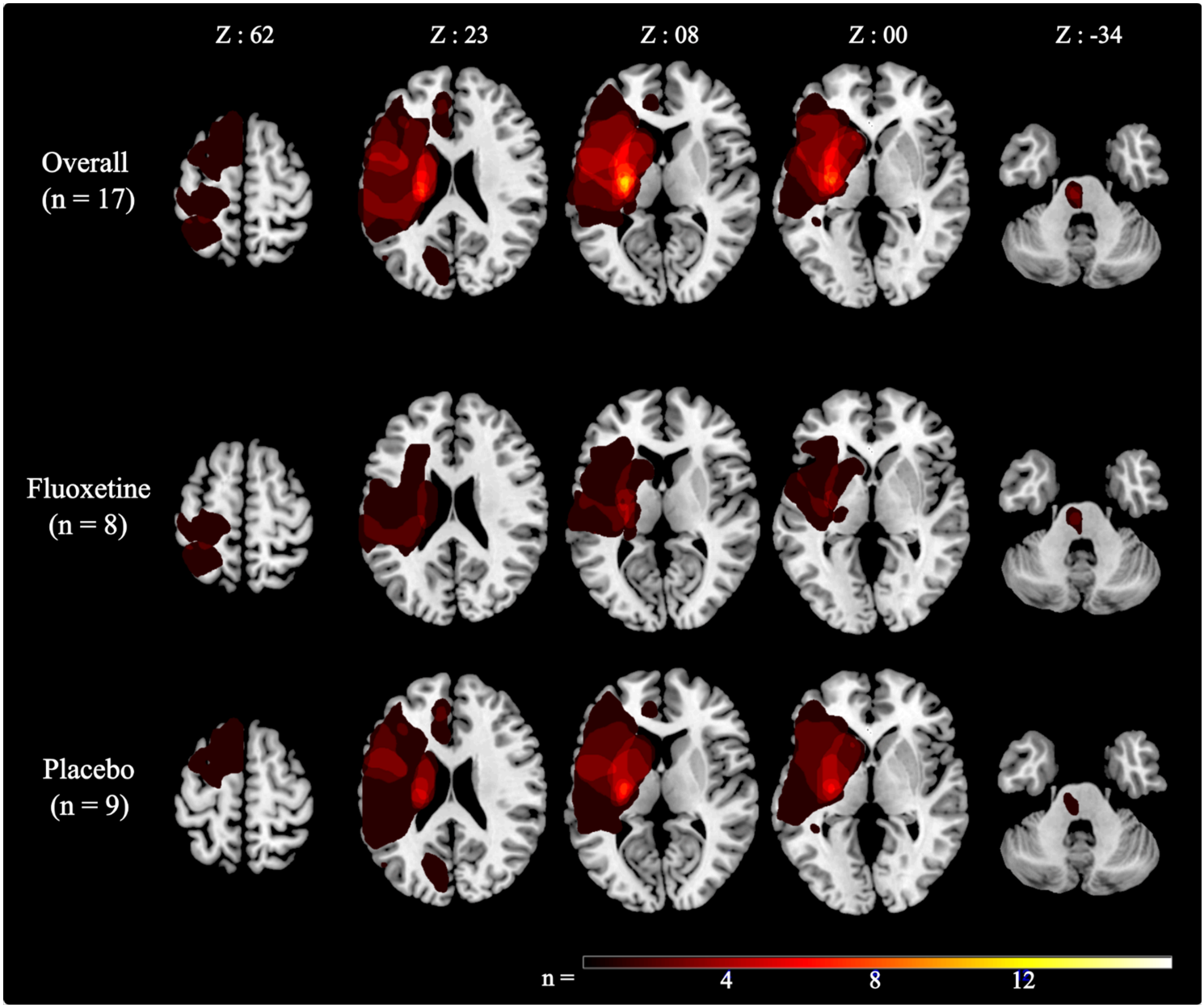


Figure 2

Map of initial ischaemic lesions The colour scale corresponds to the patient number.

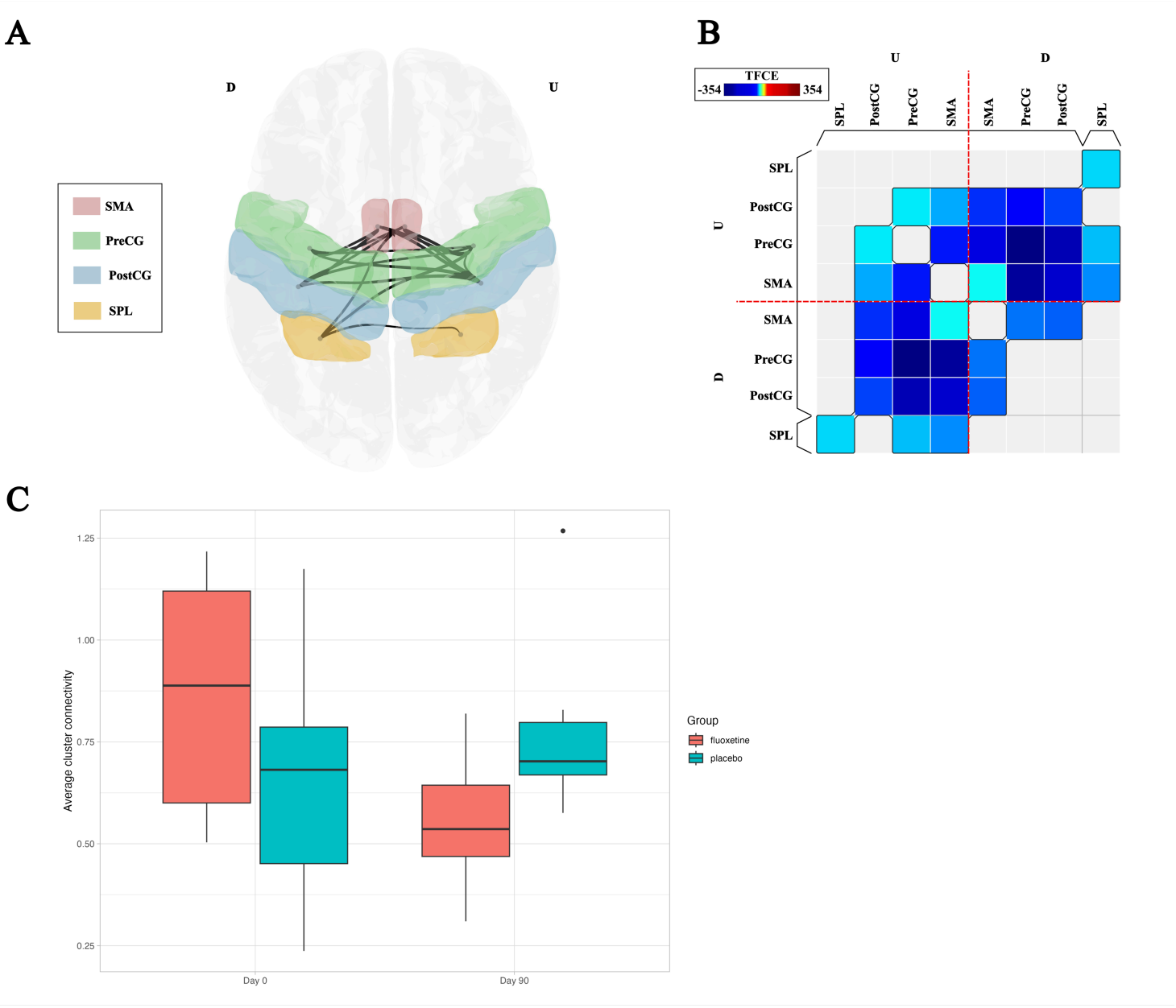


Figure 3

Resting-state FC evolution in the fluoxetine group compared with the placebo group, between Day 0 and Day 90, adjusting for the effect of age and lesion volume The figure displays the cluster of differences in functional connectivity (FC) evolution, characterised by a decrease in connectivity between bilateral motor regions. (**A)** shows the network map of the regions of interest (ROIs) included in the cluster and their FC connections. D = damaged hemisphere; U = undamaged hemisphere; SMA = juxtapositional lobule cortex; PreCG = precentral gyrus; PostCG = postcentral gyrus; SPL = superior parietal lobule. (**B)** highlights the matrix display of the FC cluster depicted in (**A)**. Yellow, orange and red indicate increasing connectivity, while blue represents decreasing connectivity. TFCE = threshold-free cluster enhancement. (**C)** shows the median of average functional connectivity of the cluster at Days 0 and 90.

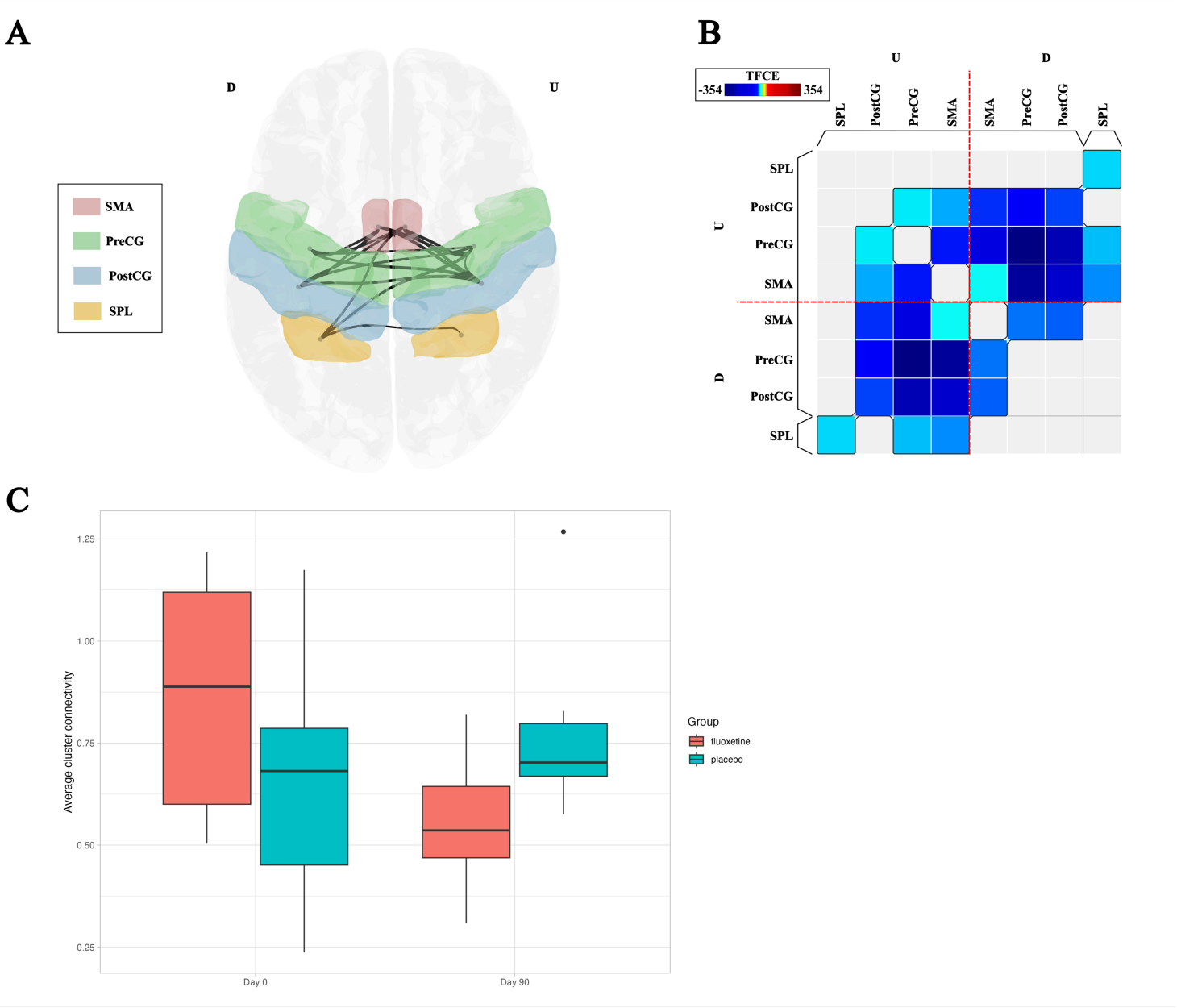


Figure 3

Resting-state FC evolution in the fluoxetine group compared with the placebo group, between Day 0 and Day 90, adjusting for the effect of age and lesion volume The figure displays the cluster of differences in functional connectivity (FC) evolution, characterised by a decrease in connectivity between bilateral motor regions. (**A)** shows the network map of the regions of interest (ROIs) included in the cluster and their FC connections. D = damaged hemisphere; U = undamaged hemisphere; SMA = juxtapositional lobule cortex; PreCG = precentral gyrus; PostCG = postcentral gyrus; SPL = superior parietal lobule. (**B)** highlights the matrix display of the FC cluster depicted in (**A)**. Yellow, orange and red indicate increasing connectivity, while blue represents decreasing connectivity. TFCE = threshold-free cluster enhancement. (**C)** shows the median of average functional connectivity of the cluster at Days 0 and 90.

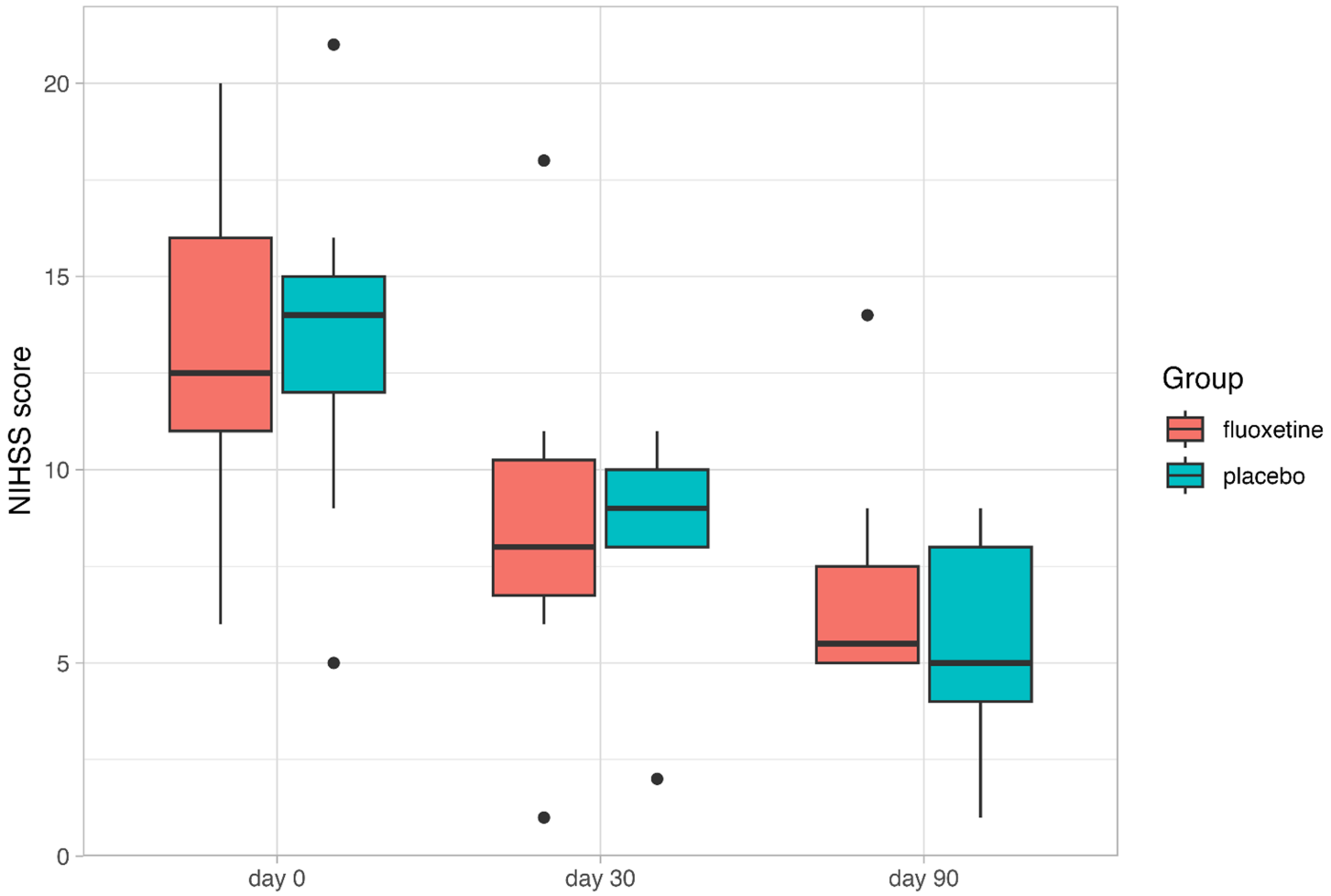


Figure 4

Median National Institutes of Health Stroke Scale (NIHSS) score at Days 0, 30, and 90

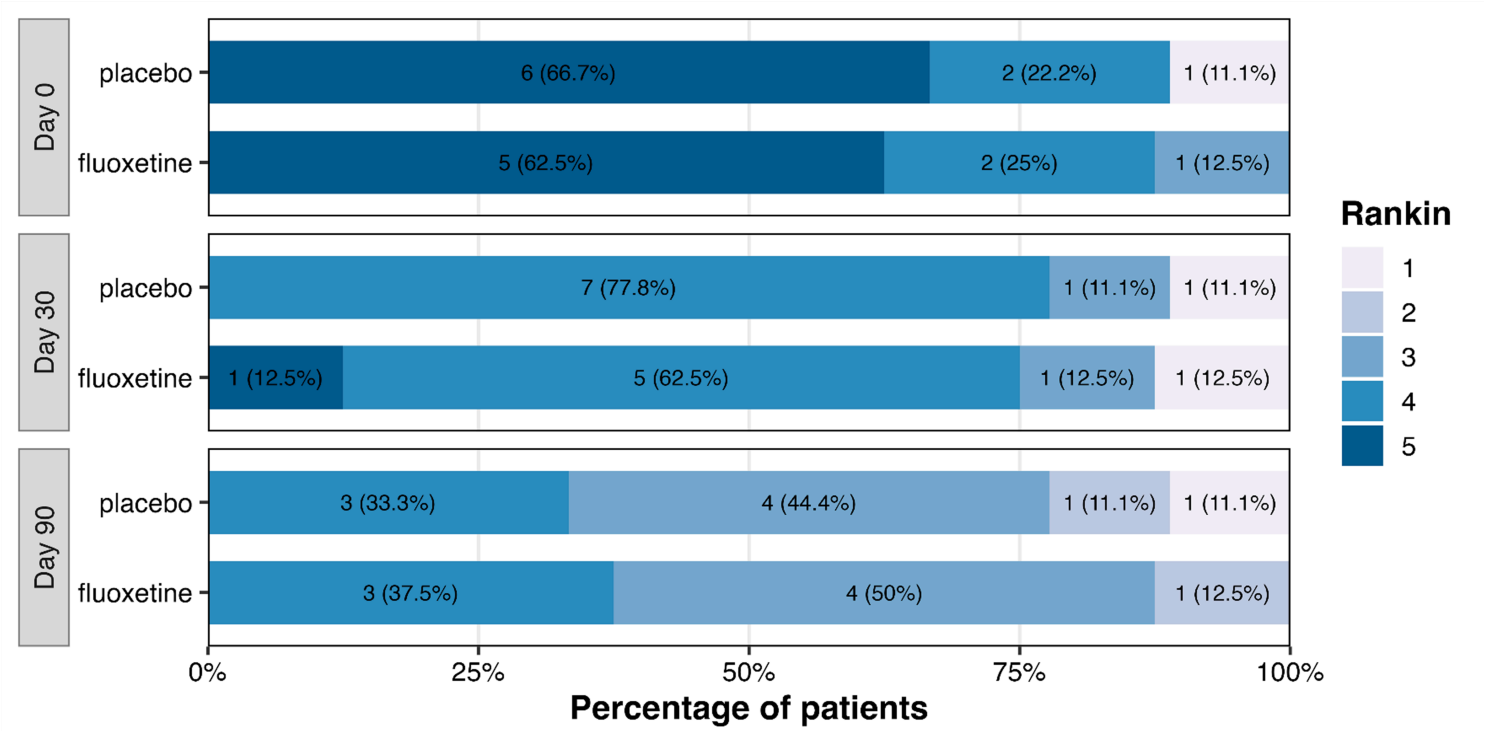


Figure 5

Distribution of Modified Rankin Scale (mRS) scores at Days 0, 30 and 90

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementarymaterialPDF.pdf
- DatabrutesRECONISE.zip
- Table1.jpg