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Altered insula modulation during salience processing in chronic spinal cord injury: A functional magnetic resonance imaging study

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ABSTRACT

Executive functions are critical for problem-solving, planning and interference control. Even in the absence of brain damages, individuals with spinal cord injury (SCI) may experience difficulties with executive functions, but the underlying neural mechanisms remain unclear. This study addressed this issue by investigating the neural correlates of interference control in SCI. Twenty-six individuals with chronic SCI and twenty-six controls performed the Flanker task during functional magnetic resonance imaging. Interaction effects between group and condition (congruent, incongruent, neutral) with respect to performance were assessed using linear mixed-effects models. Imaging data were pre-processed and between-group differences were analyzed using a general linear model. Family-wise error correction was applied at a cluster level. Spearman correlation was computed to investigate the link between performance and brain activity. Significantly lower performance in the Flanker task was recorded in individuals with SCI compared to controls and there was a significant interaction effect between group and condition, with lower performance in the neutral condition in SCI. In the left insula and right precuneus there was a significant interaction effect between group and condition (incongruent versus neutral). Flanker accuracy significantly correlated with insular activity in controls, but not in SCI. Individuals with SCI demonstrated altered condition-specific perceptual conflict and differential brain activity in regions associated with salience processing. The insula appears less engaged in supporting further cognitive processing in SCI. Findings of this study advocate for a more comprehensive assessment of cognitive changes after SCI.

Introduction

In everyday life we are confronted with a vast amount of information. Spontaneously, we filter out information which is not relevant to us and focus on the relevant aspects. The ability to overcome distraction from interfering stimuli during the processing of goal-relevant information is known as interference inhibition or interference control, which in turn belongs to inhibitory control, a core domain of executive functions crucial for problem-solving, planning and decision-making (Diamond, 2013; Cragg, 2016). Interference control is tightly related to processes of selective attention, necessary to steer the focus to the goal-relevant information (Diamond, 2013; Kinder et al., 2022).

A task widely used to measure the individuals' ability in interference control is the Flanker task (Eriksen and Eriksen, 1974), in which participants respond to a central target arrow surrounded by flanking stimuli that can be congruent, incongruent, or neutral (Kopp et al.,

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1996). This design allows for the differentiation of conflict-based interference, when flankers evoke a competing response, from distractor-based interference in the absence of directional conflict (neutral condition) (Kopp et al., 1996).

In the past years, neuroimaging studies shed light on the neural correlates of interference control. Meta-analyses including functional magnetic resonance imaging (fMRI) studies in neurologically healthy individuals have highlighted a role of the supplementary motor area (SMA), the anterior cingulate gyrus (ACG), the superior and inferior frontal and parietal cortices including the precuneus, the insula, the thalamus and the basal ganglia in inhibitory control (Wager et al., 2005; Nee et al., 2007; Li et al., 2017). The SMA and ACG are involved in the integration of information from various brain regions and conflict monitoring, respectively (Pan and Wang, 2023). The frontal and parietal cortices support top-down inhibitory control and the allocation of attention during goal-directed behavior (Corbetta and Shulman, 2002; Munakata et al., 2011). The precuneus contributes to executive functions through the interaction with frontoparietal regions (Yeager et al., 2022), while the insula plays a key role in salience detection, and serves as a hub of the central executive network (Menon and Uddin, 2010). Finally, the thalamus and basal ganglia regulate executive processes through projections towards prefrontal regions (Haber and Mcfarland, 2001).

Previous research has also found that dysfunctions of this brain system are associated with behavioral consequences in daily life, specifically impacting an adequate filtering of goal-relevant information (McDonald et al., 2002; Wylie et al., 2009; Munakata et al., 2011; Bari and Robbins, 2013; van Geest and Engelbregt, 2022). A lower performance in interference control, measured by the Flanker task, has also been reported in individuals with spinal cord injury (SCI) (Cohen et al., 2017). It is well known that a SCI may have several consequences for the affected person's life, including paralysis, bladder dysfunctions, cardiovascular and respiratory problems, pain and psychiatric disorders (National Spinal Cord Injury Statistical Center, 2014; Chamberlain et al., 2015; Sezer, 2015; Gross-Hemmi et al., 2019; Alcántar-Garibay et al., 2022). A growing number of recent studies have also reported cognitive alterations following SCI, with attention and executive functions being among the most affected domains (Cohen et al., 2017; Sachdeva et al., 2018; Sandalic et al., 2022; Moro et al., 2023; Sargent et al., 2023; Calderone et al., 2024). Cognitive functions seem to worsen from the subacute to the chronic phase of the SCI (Molina et al., 2018; Molina-Gallego et al., 2021). Potential contributing factors to developing cognitive changes are neuroinflammation and neurodegeneration, which spread beyond the initial injury site up to the brain (Khan et al., 2021; Alcántar-Garibay et al., 2022). Moreover, medication side effects, the co-occurrence of a traumatic brain injury (TBI), autonomic dysfunctions, chronic pain, sleeping disorders and cortical reorganization may contribute to cognitive changes after SCI (Sachdeva et al., 2018; Alcántar-Garibay et al., 2022). Among these factors, one potential explanation for cognitive alterations after SCI is accelerated brain aging. Supporting this, Chiaravalotti et al. found that individuals with SCI performed worse than age-matched controls across several cognitive domains, but they did not differ in performance compared to older non-injured individuals (Chiaravalloti et al., 2020a). This process may be partly mediated by injury-induced neuroinflammation, which has been proposed to promote neurodegeneration in the brain (Jure and Labombarda, 2017; Vints et al., 2023). Future research should further develop this hypothesis, by investigating a direct link between biomarkers of ageing and the brain.

The debate on the potential role of the level of the injury in the spinal cord and completeness of the lesion is still open. Some studies reported a link between these clinical variables and cognitive performance, but the majority of studies did not find a direct, significant relationship (Cohen et al., 2017; Molina et al., 2018; Sachdeva et al., 2018; Chiaravalloti et al., 2020b; Sritharan et al., 2026). However, plasticity processes of ascending and descending Wallerian degeneration and brain neural reorganization following SCI have been demonstrated (Kamble et al., 2011; Solstrand Dahlberg et al., 2018; Ziegler et al., 2018).

Neuroimaging studies have revealed that, although SCI primarily involves an injury to the spinal cord, the disconnection between body and brain, and the disruption of sensorimotor pathways are associated with functional and structural brain alterations, which are not limited to the sensorimotor cortex, but extend to areas involved in cognitive and emotional processes (Bruehlmeier et al., 1998; Turner et al., 2003; Wrigley et al., 2009; Jure and Labombarda, 2017; Pan et al., 2017; Nardone et al., 2018; Zheng et al., 2021; Wang et al., 2022; Chen et al., 2023; Scandola et al., 2024; Sritharan et al., 2025). For instance, recent resting-state fMRI studies have found alterations in the frontoparietal network, a brain network highly relevant for executive functions (Vincent et al., 2008), in individuals with SCI compared to non-injured controls (Vallesi et al., 2022; Zheng et al., 2022; Sritharan et al., 2025). These functional brain alterations after SCI likely reflect underlying neuroplastic adaptation mechanisms (Dunlop, 2008), which at the cellular level manifest as changes in synaptic efficacy, conduction velocity and neuronal excitability and inhibition (Dunlop, 2008).

Assessing brain activity during cognitive tasks allows us to identify atypical activation patterns in a clinical population compared to a control group. Using fMRI, for instance, neural mechanisms of cognitive processes can be identified by measuring the blood-oxygen-level dependent (BOLD) signal (Ogawa et al., 1990). Despite the growing number of studies reporting behavioral changes in cognition after SCI, the underlying neural correlates remain poorly understood due to significant gaps in the existing neuroimaging literature. To date, there are only few neuroimaging studies investigating brain alterations during the execution of cognitive tasks in the SCI population (Chen et al., 2016; Athanasiou et al., 2018; Lucci et al., 2019; Gao et al., 2020; Wylie et al., 2020; Vallesi et al., 2025; Sritharan et al., 2026). This limited body of work primarily focuses on motor-related cognition, such as motor imagery (Chen et al., 2016; Athanasiou et al., 2018; Gao et al., 2020), or specific subdomains like processing speed (Wylie et al., 2020), response inhibition (Lucci et al., 2019; Vallesi et al., 2025) or verbal fluency (Sritharan et al., 2026). Crucially, no fMRI study to date has investigated whether SCI alters the neural substrates dedicated to interference control. While a few recent studies have explored related executive subdomains like response inhibition, they are either constrained in their spatial resolution by the use of scalp EEG (Lucci et al., 2019), or they utilized different executive function paradigms (Vallesi et al., 2025; Sritharan et al., 2026). Consequently, because previous whole-brain fMRI studies have not targeted conflict resolution, it remains unknown whether altered interference after SCI reflects changes in specific executive or domain-general networks. Resolving this question will aid in advancing our understanding of post-injury neuroplasticity in the specific domain of interference control, and may be informative for a more comprehensive assessment of the cognitive state after SCI.

Therefore, the aim of our task-based fMRI study was to investigate functional brain changes in individuals with SCI during a Flanker task, particularly with respect to the inhibition of conflicting responses and non-conflicting interferences. We hypothesized to find both lower performance in individuals with SCI and brain activity alterations in regions associated with inhibitory control. This study may contribute to a more comprehensive assessment of cognitive function after SCI.

Materials and methods

Study design and ethical methods approval

This prospective observational study employed a case-control design. The ethical approval of the study was given by the ethics committee of Northwest and Central Switzerland (ID: 2023–02071). Before participating in the study, all participants provided written informed consent according to the guidelines of good clinical practice and the Declaration of Helsinki. We preregistered the study on ClinicalTrials.gov

(ID: NCT06309888).

Study participants

Individuals with SCI and non-injured controls participated in the study. Study participants with SCI were recruited from the Swiss Paraplegic Center in Nottwil, a specialized clinic for SCI in Switzerland. Non-injured controls were recruited through various channels including the institute's intranet and word of mouth. The sample size calculation was based on a power analysis conducted on a study comparing the results of neuropsychological assessment of individuals with SCI and controls, and is described in detail in (Sritharan et al., 2026). It returned a sample size of 25 individuals per group, which was further raised to 26 per group (Sritharan et al., 2026). With respect to the inclusion criteria, individuals with traumatic SCI between the age of 18 and 60 years, with a time since injury above 1 year, were included in the study (Sritharan et al., 2026). Participants with a diagnosis of TBI with visible brain damage on anatomical images (i.e., intracranial hemorrhages, hydrocephalus, midline shifts), as assessed by an experienced radiologist (RKV), were excluded. Further exclusion criteria were insufficient hand function (i.e., participants were asked about their ability to hold a pen) according to (Bloch et al., 2016; Vallesi et al., 2025), and diagnosis of other neurological or psychiatric disorders.

Flanker task

Participants underwent an fMRI measurement while performing a Flanker task using their dominant hand. A modified version of the Flanker task, using three stimulus conditions (Kopp et al., 1996; Fan et al., 2002), was presented in an event-related design on a screen. After a short exercise session in the MRI scanner to familiarize the participants with the MRI-compatible response device and the task, the actual Flanker task started, which was divided into three consecutive sessions containing 90 trials each and short 5 s breaks between sessions. Each trial started with a fixation cross, and was followed by the Flanker stimulus and a jittered inter-stimulus-interval, during which a blank screen was displayed (Fig. 1A). The Flanker stimulus consisted of five elements and was presented in three conditions (90 stimuli per condition; Fig. 1B): in the congruent condition, a central arrow was flanked by two arrows on each side pointing in the same direction; in the incongruent condition, the flanking arrows pointed in the opposite direction, evoking competing responses and inducing conflict (Kopp et al., 1996); and in the neutral condition, the central arrow was flanked by squares, which carry no directional information and thus produce distractor-based interference without response conflict (Kopp et al., 1996; Wang et al., 2013).

The different Flanker stimuli were presented to the participants in a randomized order. Participants were instructed to respond as fast as possible to the direction of the middle arrow by pressing the corresponding button on the response device. The task was implemented in PsychoPy® (https://www.psychopy.org/, version 2023.2.3). At the end of each 90 trials session, participants received feedback on their accuracy of the current session (percentage of correct responses) displayed on the screen, to sustain their motivation for the remaining sessions.

Clinical assessment and questionnaires

After collecting general demographic data, participants filled out questionnaires including the Numeric Pain Rating Scale (NPRS) (Edwards, 2005) and the Pittsburgh sleep quality index (PSQI) (Buysse et al., 1989) to check for an impact of pain and quality of sleep on cognitive performance (Alcántar-Garibay et al., 2022). For the SCI group, the International Standards for Neurological Classification of Spinal Cord Injury (Kirshblum et al., 2011) (ISNCSCI) examination was carried out by a healthcare professional with a test certification and the American Spinal Cord Injury Association impairment scale (AIS) level was determined. Individuals with AIS A are characterized by a complete SCI with a loss of sensations and mobility below the level of injury, while AIS B-D describe an incomplete injury with some degree of preserved motor and/or sensory functions below the level of injury (Roberts et al., 2017; Mahanes et al., 2024).

Image acquisition and processing

Neuroimaging data were acquired with a 3 T Philips Achieva scanner (Philips Healthcare, Best, Netherlands) using a 32-channel head coil.

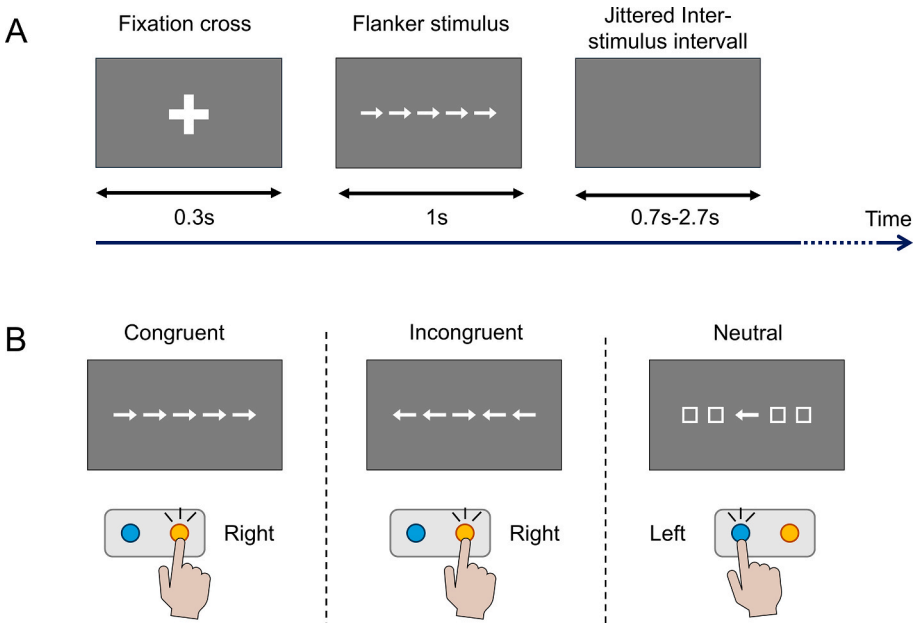

Fig. 1. Flanker task design. Panel A shows the elements of a single trial, consisting of a fixation cross with a fixed duration of 0.3 s, the Flanker stimulus with a duration of 1 s, followed by a blank screen with a jittered interstimulus interval varying randomly between 0.7 and 2.7 s. Panel B shows the three different conditions of the Flanker stimulus, which are either congruent (all arrows are pointing in same direction), incongruent (middle arrow is pointing in different direction than adjacent arrows) or neutral (middle arrow surrounded by squares), and the correct responses, respectively.

The imaging protocol consisted of a i) anatomical 3D T1-weighted scan parametrized with an echo time (TE) = 3.7 ms, repetition time (TR) = 8.1 ms, flip angle = 8°, voxel size = 1x1x1mm^3, field of view (fov) = 256x256x180mm^3 and number of slices = 180, and ii) a functional BOLD scan with TE = 30 ms, TR = 2900 ms, flip angle = 80°, voxel size = 3x3x3mm^3, fov = 240x240x159mm^3, number of slices = 53 and 285 repetitions. The scanning duration for structural scan was around 2 min and for the fMRI measurement 14 min.

Structural and functional images were preprocessed in MATLAB R2020a (The MathWorks Inc., Natick, Massachusetts) using CONN (Nieto-Castanon and Whitfield-Gabrieli, 2022) version 22 and Statistical Parametric Mapping (Friston, 2003) (SPM) 12 (http://www.fil.ion.ucl.ac.uk/spm). The preprocessing pipeline included realignment, slice timing correction, outlier detection (global BOLD signal change above 5 standard deviations or more than 0.9 mm framewise displacement (Power et al., 2014)), segmentation, normalization into Montreal Neurological Institute (MNI) space, and spatial smoothing with a Gaussian kernel of 8 mm full width half maximum (Nieto-Castanon, 2020). Quality control measures, including number and proportion of invalid scans, mean motion, degrees of freedom and normalized space to functional and anatomical accuracy, were computed with the CONN toolbox (Morfini et al., 2023). Individuals for whom the quality metrics deviated for more than 3 interquartile ranges below the 1st quartile or above the 3rd were considered as extreme outliers (Morfini et al., 2023) and were therefore removed from the imaging analysis (Supplementary Fig. S1).

Imaging analysis

BOLD signal of correct trials was compared between the two groups using a general linear model (GLM) in SPM. In the first-level analysis, flanker stimuli (congruent, incongruent, neutral) were modeled as delta functions, and convolved with a canonical hemodynamic response function at each stimulus onset. The onsets and durations of fixation crosses and jittered interstimulus intervals, as well as six realignment parameters (three translations and three rotations) to account for each individual's head motion (Friston, 2003; Johnstone et al., 2006), were included in the design matrix as additional regressors. Moreover, a temporal high pass filter of 128 s was applied to remove slow signal drifts, and serial correlations were accounted for by using an autoregressive AR(1). T-contrasts were employed to evaluate three contrasts, in particular (i) the commonly assessed "Flanker effect" given by the contrast incongruent > congruent (Zhu et al., 2010), (ii) the contrast incongruent > neutral, which measures the differential activity between the processing of conflicting and non-conflicting interferences, and (iii) the contrast neutral > congruent, targeting the differential activity between the processing of non-conflicting interferences and facilitation. Contrast images between the two groups (SCI and non-SCI) were compared in the second-level analysis using a two-sample *t*-test. The cluster-forming height threshold was set to $p = 0.005$ to ensure an appropriate balance between Type I (false positive) and Type II (false negative) error rates for small sample sizes (Lieberman and Cunningham, 2009; Roiser et al., 2016; Cremers et al., 2017) and the minimum cluster size was 100 voxels. Results were corrected for multiple comparisons using family-wise error (FWE) correction $p_{FWE} < 0.05$ at a cluster-level in the whole brain. We also computed activation maps for the three contrasts incongruent > congruent, incongruent > neutral and neutral > congruent for each group (SCI and non-SCI) separately to identify activated regions in the single groups.

Statistical analysis

Questionnaire data and behavioral data from the Flanker task were analyzed in R (version 4.4.1). For the behavioral data, the outcome variables of interest were the accuracy, defined as percentage of correct responses, and the average response time to react to a stimulus. As each participant responded to several stimuli, the dataset followed a repeated measures design. To assess potential interaction effects between Group (SCI vs. non-SCI) and Condition (congruent, incongruent, neutral) with respect to the outcome variables, separate linear mixed-effects models were fitted for accuracy and response time using the *lme4* package in R. In addition, accuracy and response time were combined into the inverse efficiency score, defined as the mean reaction time divided by the accuracy (Townsend and Ashby, 1978; Guay et al., 2026), as a further outcome variable (Supplementary material). For all models, fixed effects included Condition X Group interaction, and random intercepts were calculated for each subject. Age was added as covariate of no interest. Fixed effects were assessed using type III analysis of variance (ANOVA) with Satterthwaite's method (Satterthwaite, 1941; Schaalje et al., 2002). Statistical significance was determined using F-tests. To assess the magnitude of effects, partial η^2 were computed for the effect sizes, with η^2 values between 0.01 and 0.06 representing small, values between 0.06 and 0.14 medium, and $\geq$ 0.14 large effects (Cohen, 2013; Lakens, 2013). For significant results in the ANOVA, magnitude and precision of group and condition differences were further characterized using estimated marginal means (EMMs) with 95% confidence intervals, derived using the *emmeans* R-package with the Kenward-Roger degree-of-freedom approximation (Searle et al., 1980). Post-hoc pairwise contrasts between groups within each flanker condition were computed on the EMMs and correction for multiple comparisons was conducted with Holm's method (Searle et al., 1980; Haynes, 2013). The adjusted p-value is described with p_{adj}. Behavioral outliers, defined as a deviation in the outcome variable for more than three standard deviations from the group mean, were removed from the behavioral analysis (see Results).

Correlations between brain activity of regions showing significant effects in the second-level imaging analysis, and differential Flanker accuracy were computed for both groups separately using partial Spearman correlation with age as covariate. As a proxy for brain activity, beta values were extracted for each individual from the significant clusters of the group comparison using the MARSeille Boîte À Région d'Intérêt (MarsBaR) toolbox for SPM (https://marsbar-toolbox.github.io/). To mirror the BOLD contrast, the differential Flanker accuracy was also calculated as the difference of accuracy between the respective conditions for each individual. The correlation coefficient is denoted with ρ. Moreover, the correlation coefficients were compared between groups applying Fisher's r to z transformation. As exploratory analyses, the accuracy in the Flanker task was correlated with the current pain level and the PSQI score for each group (SCI and non-SCI) individually (Supplementary material).

Given the long task duration, potential effects of fatigue were investigated by assessing a change in accuracy over the three subsequent sessions in both groups. Thereby, a linear mixed-effects model was implemented with the interaction Group X Session number as fixed effects, subject as random effects, and age as covariate. Post-hoc tests were computed using estimated marginal means and correction for multiple comparisons was conducted with Holm's method (Searle et al., 1980; Haynes, 2013).

Moreover, exploratory subgroup analyses between SCI individuals with AIS A, AIS D and non-injured controls were conducted, as well as between individuals with complete, incomplete SCI and non-injured controls (Supplementary material). The outcome variables of interest were compared between the three groups using a Kruskal-Wallis rank sum test due to violation of homogeneity of variances. The test statistics are denoted with χ^2 and the effect size with η^2 (Cohen, 2013). Post-hoc tests were conducted using Dunn's test and correction for multiple comparison was carried out with the Holm's method (Dunn, 1964; Haynes, 2013). The adjusted p-value is described with p_{adj}.

Results

Participant characteristics

The study sample included 26 age- and sex-matched participants with SCI and 26 individuals without SCI. For the behavioral analysis with accuracy as outcome variable, there was one outlier per group, leading to 25 SCI individuals (mean age = 45.5 ± 11.1 years) and 25 controls (mean age = 43.6 ± 11.4 years). With respect to response times of correct trials, there was no outlier. Demographic and clinical characteristics are presented in Table 1, and further details were previously described in (Sritharan et al., 2026).

Behavioral results

On average, individuals without SCI showed an accuracy in the Flanker task of 98%±1.2% and individuals with SCI 96.1%±3.7% across the three conditions. There was a significant main effect of group (p = 0.015, F = 6.427, η^2=0.12), with SCI individuals scoring lower than controls by an estimated 2.0% (95% CI = [0.41%, 3.54%]). There was also a significant interaction effect for accuracy between group and Flanker condition (p = 0.049, F = 3.121, η^2=0.06) (Fig. 2A). Post-hoc tests revealed a significant between-group difference in the neutral condition (difference = 3.0%, 95% CI = [0.34%, 5.72%], p_{adj} = 0.014) but not in the incongruent (difference = 1.3%, 95% CI = [-1.35%, 4.03%], p_{adj} = 0.616) or the congruent (difference = 1.6%, 95% CI = [-1.13%, 4.25%], p_{adj} = 0.578) condition between the two groups. SCI individuals scored lower than controls across all three conditions. The response time of correct trials was 0.663 s ± 0.102 s for the SCI group and 0.616 s ± 0.081 s for the non-SCI group. There was no significant group effect (p = 0.120, F = 2.503, η^2=0.05) and no interaction effect between group and condition (p = 0.090, F = 2.471, η^2=0.05) with regards to response time (Fig. 2B). Similarly, there was neither a significant main effect of group nor an interaction effect in the model fitted for the inverse efficiency score (Supplementary Fig. S2).

Correlating the overall accuracy in the Flanker task with the current pain level and the PSQI score for each group (SCI, non-SCI) individually revealed a significant association of higher pain levels and lower Flanker accuracy in the non-SCI group, but no other significant correlations (Supplementary Fig. S3). Comparing the performance across the three subsequent sessions, the accuracy increased over time (p = 0.009), with individuals with SCI showing a significant improvement in accuracy in the 2nd and 3rd session compared to the 1st one (Supplementary Fig. S4). For the subgroup analysis with respect to AIS levels, there was a significantly lower performance in the AIS A group compared to AIS D (p_{adj} = 0.037) and non-injured controls (p_{adj} = 0.009), and no difference in response times (Supplementary Fig. S5). With respect to the subgroup analysis comparing individuals with complete SCI, incomplete SCI and non-injured controls, there was a significantly lower accuracy in individuals with complete SCI compared to non-injured controls (p_{adj} = 0.010), but neither a significant difference in accuracy between complete and incomplete SCI nor in response time across all three groups (p = 0.112) (Supplementary Fig. S6).

Table 1
Demographic and clinical characteristics.

	Non-injured individuals (N = 26)	Individuals with spinal cord injury (N = 26)	p-value
Age (years)	43.1 (11.5)	45.8 (11.0)	0.290
Sex, female/male (n)	8/18	8/18	1
Time since injury (years)	–	13.3 (11.1)	–
Handedness (left/right)	1/25	5/21	0.193
Current pain NPRS	0.3 (0.5)	2.7 (2.2)	**<0.001**
Pain in the last 7 days NPRS	0.5 (0.7)	3.1 (2.3)	**<0.001**
Sleep quality PSQI	4.1 (1.9)	6.3 (4.0)	**0.018**
AIS level	–		–
A		11	
B		1	
C		2	
D		12	
Level of injury	–		–
C1-C4		4	
C5-C8		8	
T1-S5		14	

Standard deviation in parentheses.
AIS: American Spinal Cord Injury Association impairment scale, NPRS: numeric pain rating scale, PSQI: Pittsburgh sleep quality index.

Imaging results

Four SCI subjects posed extreme outliers with respect to the imaging quality control measures (Supplementary Fig. S1) and were therefore removed from the imaging analysis, leading to a sample size of 22 individuals with SCI and 26 individuals without SCI. With respect to the within-group activation in the contrast incongruent > congruent, there was a significant cluster in the supplementary motor cortex (p_{FWE} = 0.006) and the left superior parietal lobule (p_{FWE} = 0.001) in non-injured controls (Supplementary Table S1 and Fig. S7). For the contrast incongruent > neutral the non-SCI group showed significant clusters in the right superior frontal gyrus (p_{FWE} < 0.001) and the right inferior occipital gyrus (p_{FWE} = 0.045) (Supplementary Table S2 and Fig. S8). With respect to the contrasts incongruent > congruent and incongruent > neutral, there was no significant cluster for the SCI group. For the contrast neutral > congruent non-injured controls did not show significant activation in any brain region, while in individuals with SCI the left (p_{FWE} < 0.001) and right fusiform gyrus (p_{FWE} = 0.005) and the right middle occipital gyrus (p_{FWE} = 0.028) significantly activated (Supplementary Table S3 and Fig. S9).

With respect to the between-group comparisons, the contrast incongruent > neutral and non-SCI > SCI revealed a significant interaction effect in the BOLD signal with a peak in the left insula (p_{FWE} = 0.033, cluster size = 561, peak MNI coordinates = -40, −18, 10) (Fig. 3A and B) and in the right precuneus (p_{FWE} = 0.010, cluster size = 728, peak MNI coordinates = 14, −68, 40) (Fig. 3C and D). For both the insula (Fig. 3B) and the precuneus (Fig. 3D), non-injured controls exhibited higher activation during the incongruent condition compared to the neutral condition, while individuals with SCI showed higher activation during the neutral compared to the incongruent condition. With respect to the contrasts incongruent > congruent and non-SCI > SCI as well as neutral > congruent and non-SCI > SCI, there were no significant interaction effects in any brain region.

Correlation of imaging and behavioral performance

For the correlational analysis, the previously mentioned behavioral (n = 2) and imaging outliers (n = 4) were removed, leading to a sample size of n = 25 for the controls and n = 21 for the SCI individuals. When correlating the beta estimates from the contrast incongruent > neutral with the difference in accuracy between the incongruent and neutral condition in each group separately, there was a significant negative correlation in the left insula for individuals without SCI (p = 0.001, ρ=-0.628) but not for individuals with SCI (p = 0.693, ρ=-0.094) (Fig. 4A). Particularly, in individuals without SCI a higher difference in the insular activity between the incongruent and neutral condition was associated with a more negative difference in accuracy between the incongruent and neutral condition. The comparison of the two correlation coefficients revealed a significant difference between the two groups (p = 0.043, z = -2.026). In the right precuneus, neither in individuals with SCI (p = 0.779, ρ=0.067) nor in non-injured controls (p = 0.128, ρ=-0.319) there was a significant correlation (Fig. 4B).

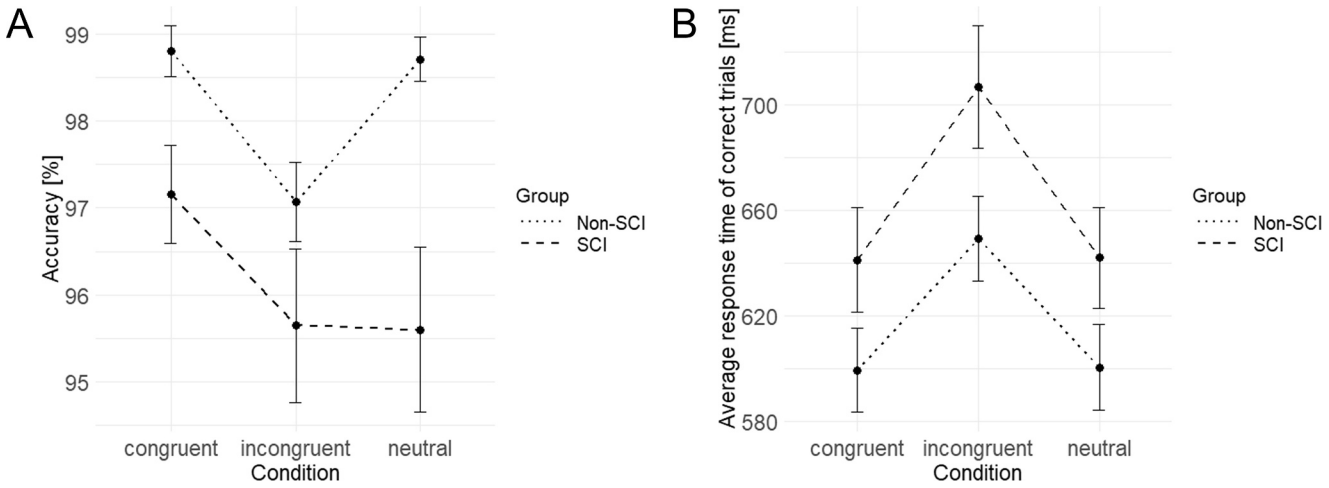

Fig. 2. Behavioral results in the Flanker task. Panel A shows the accuracy separately for the SCI (n = 25) and non-SCI (n = 25) group for the three different conditions of the Flanker task. There was a significantly lower performance in the SCI group (p = 0.015) and an interaction effect between group and condition with respect to accuracy (p = 0.049). Panel B shows the response time of the correct trials for individuals with (n = 26) and without SCI (n = 26) depending on the Flanker condition. There was neither a significant group (p = 0.120) nor an interaction effect with respect to response time (p = 0.090). Points indicate the mean and bars overlaid on the points indicate error bars.

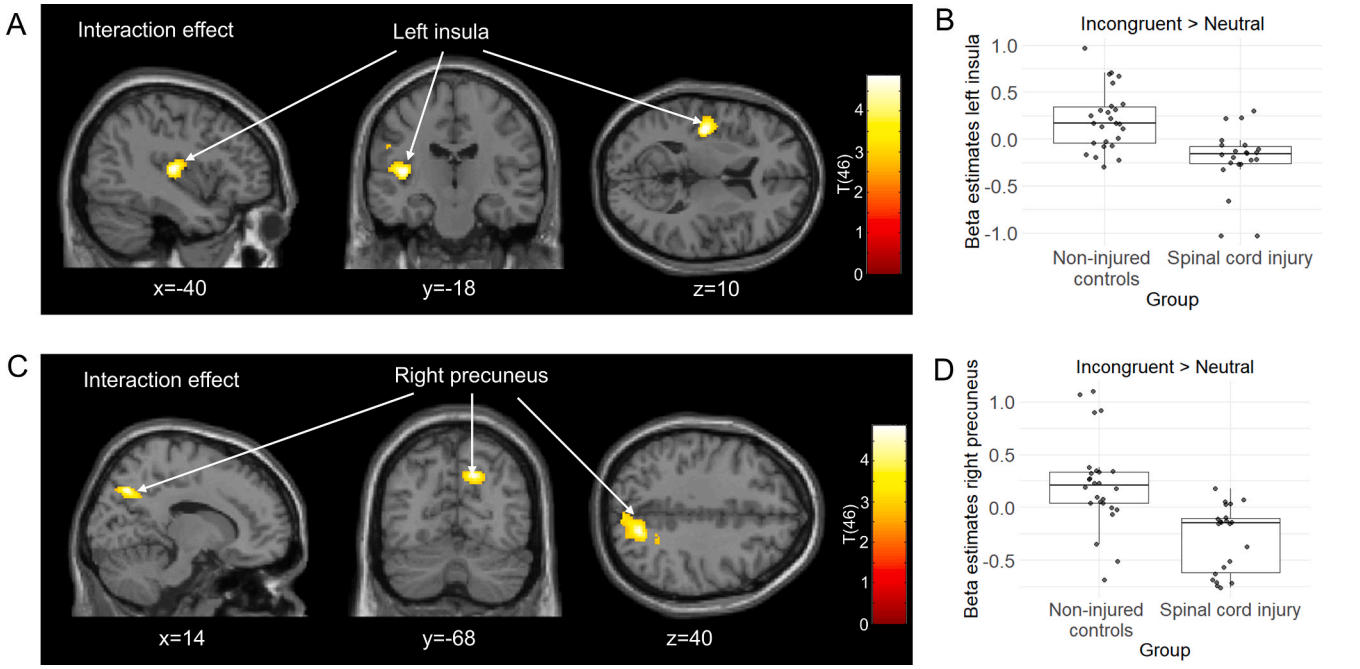

Fig. 3. Response interference-related brain activity. The figure illustrates the imaging contrast incongruent > neutral and non-SCI > SCI during the Flanker task. Panel A shows a significant interaction effect in the blood-oxygen-level dependent (BOLD) signal with peak in the left insula between the incongruent and the neutral condition between individuals with (n = 22) and without SCI (n = 26) ($p_{family\text{-}wise\ error(FWE)} = 0.033$). Panel B depicts the difference in beta estimates in the left insula between the incongruent and neutral condition for each group separately. Panel C shows the 2nd significant interaction effect with peak in right precuneus for the same contrasts ($p_{FWE} = 0.010$). The difference in beta estimates between the incongruent and neutral condition in the precuneus is displayed in panel D for both groups.

Discussion

In the presented task-based fMRI study on interference control using a Flanker task in individuals with chronic SCI we demonstrated: (i) a significantly lower accuracy in the SCI group compared to non-injured controls, and a significant Group X Condition interaction in the accuracy, with SCI individuals exhibiting poorer accuracy in the neutral condition, (ii) a significant interaction of the brain activity in the left insula and right precuneus for the contrasts incongruent > neutral condition and non-SCI > SCI, (iii) a negative correlation of insular activity in the contrast incongruent > neutral and differential performance in individuals without SCI, but not in the SCI group.

Lower performance in the spinal cord injury group

We found lower accuracy in individuals with SCI compared to controls during the Flanker task, which is in line with previous studies on inhibitory control using, for instance, the Stroop task (Wecht et al., 2012; Pozzato et al., 2023). Moreover, we found a significant interaction effect between the Flanker conditions and the group. While the

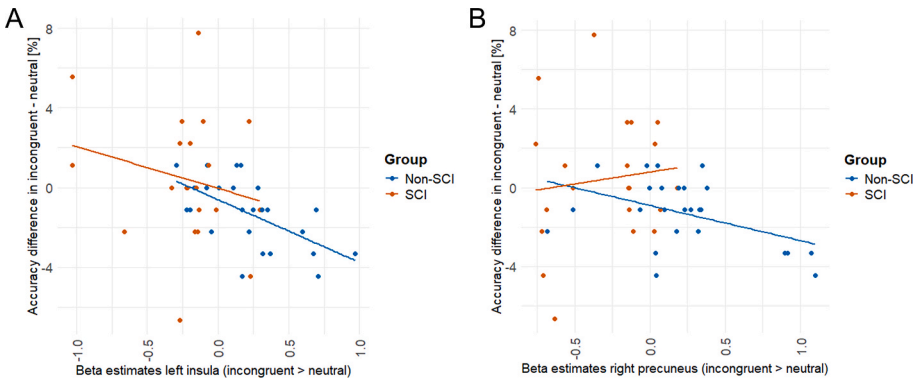

Fig. 4. Correlation between differential brain activity and Flanker accuracy. Panel A shows the Spearman correlation of beta estimates of the contrast incongruent > neutral in the left insula with the difference in accuracy between the incongruent and neutral condition in both groups individually using age as covariate. There was a significant correlation in the group of non-injured controls (n = 25) (p = 0.001, ρ=-0.628) but not in the SCI group (n = 21) (p = 0.693, ρ=-0.094) for the left insula. Panel B depicts the correlation for the right precuneus. There is no significant correlation in individuals without SCI (p = 0.128, ρ=-0.319) and with SCI (p = 0.779, ρ=0.067) for the right precuneus.

differences in accuracy between individuals with SCI and non-SCI were similar for both the congruent and the incongruent condition, the accuracy substantially differed in the neutral condition, with lower performance in the SCI group. This pattern of results does not support the presence of broad inhibitory control deficits in the SCI group, and caution is warranted in interpreting these findings as evidence of impaired response conflict inhibition. Rather, the results suggest that individuals with SCI may show condition-specific difficulties in interference control, particularly in contexts where the cognitive demand is perceived as low. Comparison with previous literature is limited by differences in task design. Cohen et al. found lower overall accuracy in the Flanker task in individuals with SCI compared to non-injured controls, but did not include a neutral condition, precluding comparability with the present findings (Cohen et al., 2017).

In the neutral condition of the Flanker task, the target arrow was surrounded by squares, elements which do not carry task-relevant directional information. It is known that stimuli resembling the target (e.g., arrows as flankers) attract more attention than neutral stimuli (e.g., squares as flankers) (Duncan and Humphreys, 1989; Li and Lou, 2019). The lower accuracy in the neutral condition in the SCI group may therefore seem counterintuitive, but could reflect a reduction in arousal during conditions perceived as less demanding. Alternatively, even though the neutral flankers do not resemble the target stimulus, they may still introduce a form of perceptual interference (Wang et al., 2013), and their presence may have an adverse, distracting effect on the processing of the direction of the central arrow. Taken together, these findings suggest that individuals with SCI may be more sensitive to perceptual interference even in the absence of conflicting directional information, though this interpretation should be treated with caution given the specificity of the effect to a single condition.

Overall, the effect size of the group effect with respect to accuracy was in the medium range, and the differences in accuracy were rather subtle, as the two groups differed only in few percentage points. The reported effect sizes based on the non-centrality parameter method are limited by imprecision and should be interpreted with caution (Steiger, 2004; Morey et al., 2016). A previous study pointed out that motor demands required for reaction time-based cognitive tasks, such as the Flanker task, may artificially reduce performance in these tasks in individuals with SCI (Lee et al., 2021). Importantly, no significant interaction effect or main effect of group was found with respect to the response time, and all effect sizes concerning response time were small – though some degree of subjectivity remains in the exclusion criterion based on pen-holding ability, which may not fully capture residual upper limb motor differences between groups. Reduced motor abilities in SCI, if present, would be expected to slow down response time (Lee et al., 2021), adding evidence that our results are likely not biased by such confounds (Supplementary Fig. S5).

Due to the tight link between interference control and attention (Wei et al., 2013; Kamali-Ardekani et al., 2022), our results may also indicate altered selective attention, as individuals with SCI may have more difficulties focusing their attentive resources solely on the middle arrow. In this regard, a limitation inherent to the Flanker task is that it does not allow for a clear disentanglement of conflict processing and selective attention (Freitas and Clark, 2015; Algom and Chajut, 2019). Indeed, several models suggest that, upon the detection of a conflict, interference control mechanisms are activated that operate through the modulation of selective attention (MacDonald et al., 1979; Botvinick et al., 2001; Egner and Hirsch, 2005). It is then possible that the lower performance reported in our SCI group derives from an altered interplay between perceptual interference and attention modulation.

The correlational analysis between the Flanker accuracy and both the PSQI and the pain score only showed a significant negative correlation between pain score and accuracy in individuals without SCI, which is supported by literature suggesting that pain may have a negative impact on cognitive functioning (Moriarty et al., 2011). The lack of associations with sleep quality may also be limited by the small sample size in the correlational analysis, or by the fact that overall sleep quality was not severely affected in the two groups. Future studies could investigate this link with a larger sample size and with more specific and objective measures of sleep quality. Therefore, an effect of these potential contributing factors (Alcántar-Garibay et al., 2022) on cognitive performance cannot be excluded. With respect to the long task duration of the Flanker task and potential effects of fatigue, we found that performance increased across sessions in the SCI group, therefore suggesting a training effect rather than fatigue. Moreover, our subgroup analysis revealed that individuals characterized by AIS level A showed significantly lower performance than SCI individuals with AIS D and non-injured controls. The lower accuracy in the AIS A group seems to be in line with the lower overall functional outcomes associated with a complete SCI (Wilson et al., 2012, 2014; Adegeest et al., 2022; Mahanes et al., 2024). However, these results have to be interpreted carefully, as the subgroup analysis only included a small number of individuals and may therefore introduce selection bias. Studies with a higher number of participants should verify the potential link between AIS level and interference control.

Altered brain activity patterns and performance associations

Based on the within-group activation maps of the imaging contrasts involving the incongruent condition of the Flanker task, we verified that regions previously associated with conflict resolution and interference control were activated in non-injured individuals (Wager et al., 2005;

Nee et al., 2007; Li et al., 2017). However, we did not observe the same activations in the SCI group, implying that processing of conflicting information seems to be altered. Interestingly, we found differential activity in brain regions related to visual processing in individuals with SCI for the contrast neutral > congruent, suggesting that people with SCI may process these two conditions differently. Differential activation for neutral > congruent was absent in the group of non-injured controls. With respect to the between-group differences, the contrasts incongruent > neutral and non-SCI > SCI revealed a significant interaction in the BOLD signal of the left insula and right precuneus. These activations mirrored the interaction Group X Condition seen in the behavioral data. Individuals without SCI activated these two regions more during the incongruent compared to the neutral condition, while in SCI participants there was a higher activation of these regions during the neutral compared to the incongruent condition. The insula and precuneus were identified in previous meta-analyses to be involved in conflict processing and interference control in healthy individuals (Wager et al., 2005; Nee et al., 2007; Li et al., 2017). These two regions also exhibited altered patterns of brain activity during the execution of other cognitive tasks targeting executive functions in individuals with SCI (Vallesi et al., 2025; Sritharan et al., 2026).

The precuneus is involved in a range of cognitive processes, including self-referential processing and episodic memory (Cavanna and Trimble, 2006; Dadario and Sughrue, 2023). More specifically, the right precuneus was shown to be involved in spatial attention (Sturm et al., 2006), which is highly relevant for the Flanker task (Yantis and Johnston, 1990; Schneider, 2019; Kewan-Khalayly and Yashar, 2022). Interestingly, several morphometric studies have found changes in the precuneus in individuals with SCI (Solstrand Dahlberg et al., 2018; Li et al., 2024; Diana et al., 2025). However, the absence of a correlation between the Flanker task performance and the precuneus activity in both the SCI and the control group suggests that the precuneus modulation may not directly reflect conflict-related processing, but rather broader task engagement mechanisms (Zhang and Li, 2010; Utevsky et al., 2014).

Studies applying similar tasks of interference control and selective attention have demonstrated higher activation of the insula during the incongruent relative to the congruent or neutral condition in healthy individuals (Kelley et al., 2013; Wei et al., 2013). The insula has different functions, among them the detection of salient stimuli (Menon and Uddin, 2010). A previous study in neurologically healthy individuals showed that the insular activity increased with task difficulty in tasks involving perceptual decision-making, therefore implying that the insula is sensitive to the difficulty of a perceptual decision (Ho et al., 2009; Lamichhane et al., 2016; Billeke et al., 2020; Reichenbach et al., 2025). As in our study non-injured controls activated the insula more during the incongruent compared to the neutral condition, this may suggest that the insula rates the incongruent stimulus as more difficult compared to the neutral one. In individuals with SCI, however, the insula activates more during the neutral condition compared to the incongruent condition, and the accuracy in the neutral and incongruent condition are similarly low, potentially indicating an altered judgement of perceptual difficulties. With respect to the left lateralization of the insula activity, several studies described the involvement of the left insula in executive control and inhibition (Späti et al., 2014; Hung et al., 2018; Varjačić et al., 2018; Vallesi et al., 2025), aspects which are substantial for the Flanker task. However, the majority of our study participants were right-handed, therefore a potential effect of handedness on the left lateralization cannot be fully excluded.

Moreover, we found a significant association between Flanker performance and insular activity in the control group, similar to previous literature (Wager et al., 2005). This brain-behavior relationship was absent in individuals with SCI, implying that there might be lower engagement of the insula with respect to conflict- and task-difficulty related processing. Previous neuroimaging studies have reported structural and functional changes in the insula after SCI (Yoon et al., 2013; Jutzeler et al., 2016; Nardone et al., 2018; Karunakaran et al., 2019; Wang et al., 2019; Chen et al., 2023), and these changes have been associated with pain processing (Yoon et al., 2013; Jutzeler et al., 2016; Wang et al., 2019; Sritharan et al., 2025). We recently showed altered functional connectivity of the insula in individuals with SCI (Sritharan et al., 2026), and proposed that its role of *switch* on the central executive network may be affected (Menon and Uddin, 2010; Namkung et al., 2017; Molnar-Szakacs and Uddin, 2022). Upon detection of a salient event, the insula acts as a switch for the central executive and the default mode network to facilitate access to cognitive resources, enabling further processing of this event (Sridharan et al., 2008; Menon and Uddin, 2010). Crucially, while previous literature consistently emphasizes the engagement of the frontoparietal control network, including the prefrontal and anterior cingulate cortices cortex during executive functioning (Vincent et al., 2008; Niendam et al., 2012), we did not observe altered activity patterns in these regions. Instead, our findings were confined to the insula and precuneus. This localized pattern suggests that individuals with SCI might manifest disruptions in more generalized processes related to the execution of the Flanker task, such as salience processing, rather than a deficit in executive control per se. This aligns with the role of the insula as a hub (Sridharan et al., 2008; Menon and Uddin, 2010) and the disrupted functional connectivity and morphometric alterations concerning the salience network after SCI (Hawasli et al., 2018; Nardone et al., 2018). A limitation of the present study concerns the reduced statistical power of the neuroimaging analysis, resulting from the removal of several extreme outliers based on quality control measures. To balance Type I and Type II error rates, and given the limited sample size, a cluster-forming threshold of $p = 0.005$ was applied following (Lieberman and Cunningham, 2009; Cremers et al., 2017), rather than the more conservative $p = 0.001$ (Eklund et al., 2016), as overly stringent thresholds substantially increase the risk of false negative errors in small samples (Ge et al., 2021). All reported clusters survived FWE correction at the cluster level ($p_{FWE} < 0.05$), yet findings should be interpreted with caution and replicated in larger samples. It is worth noting that our study did not include a control task targeting a different cognitive domain, and we cannot completely rule out that the observed results reflect overall cognitive changes rather than alterations specifically linked to executive functions. Nevertheless, the significant correlation between Flanker performance and insular activity speaks in favor of the specificity of these findings. Future studies should further elucidate the brain mechanisms of cognitive changes in SCI with a comprehensive neuroimaging assessment of distinct cognitive functions.

Translational considerations

In this study, we examined behavioral and brain alterations during a Flanker task in individuals with SCI. The domains targeted in the Flanker task represent only some aspects of cognition, and therefore do not capture overall cognitive abilities. The statistically significant group difference of around 2% in accuracy indicates a subtle disparity in individuals with SCI compared to non-injured controls. Importantly, statistical significance does not necessarily imply clinical relevance (Jakobsen et al., 2014). Especially due to a lack of normative data for the Flanker task, we cannot judge whether the measured differences are clinically relevant for individuals with SCI. Nevertheless, the findings suggest nuanced alterations in condition-specific conflict and salience processing during the neutral condition in individuals with SCI, which support the need to integrate cognitive assessments in the clinical routine. These results may therefore contribute to a more nuanced characterization of cognitive functioning in this population, particularly in individuals who do not fall below conventional neuropsychological cut-offs, but may nonetheless be prone to emerging cognitive difficulties. Problems with cognitive processes in individuals with SCI are already known from the literature (Sandalic et al., 2022). In addition, it has been found that cognitive abilities are linked to the quality of life in

people with SCI (Houldsworth et al., 2023), and that cognitive factors are associated with activities of daily living (Babu et al., 2024; Yun et al., 2024). The present study did not include information on activities of daily living, hence their link with cognitive functions in SCI could not be experimentally examined.

Taking these behavioral and brain alterations into consideration, along with known contributing factors such as medication side effects or pain (Alcántar-Garibay et al., 2022), we advocate for a more comprehensive assessment of cognitive functioning in SCI, as they are relevant to functional outcomes and daily living activities.

In this Flanker study, larger perceptual conflict during the neutral condition, along with brain activity alterations in regions associated with salience processing, were found in individuals with chronic SCI. The link between performance and insular activity in non-injured controls emphasized the role of the insula as a salience processing area, whereas in individuals with SCI the insula appears less engaged in supporting further cognitive processing, which is manifested as lower performance. This study adds further evidence to the relationship between cognitive changes in individuals with SCI and underlying brain alterations in cognitive areas, and calls for a systematic evaluation of the cognitive state after SCI.

Data availability

The data of this study are available from the corresponding author on reasonable request.

CRediT authorship contribution statement

Jothini Sritharan: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Conceptualization. **Lorenzo Diana:** Writing – review & editing, Methodology. **Vanessa Vallesi:** Writing – review & editing, Methodology. **Nicola Brunello:** Writing – review & editing. **Rahel Oertli:** Writing – review & editing. **Patrizia Dall'Acqua:** Writing – review & editing. **Inge Eriks-Hoogland:** Writing – review & editing, Investigation. **Anke Scheel-Sailer:** Writing – review & editing, Conceptualization. **Maddalena Beccherle:** Writing – review & editing. **Valentina Moro:** Writing – review & editing, Methodology. **Rajeev K. Verma:** Writing – review & editing, Supervision, Investigation, Conceptualization. **Giuseppe A. Zito:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this manuscript the authors used ChatGPT (GPT-5.2, OpenAI) for assistance in language editing. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroscience.2026.07.039.

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