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Effective connectivity analysis of resting-state mentalizing brain networks in spinocerebellar ataxia type 2: A dynamic causal modeling study

Giusy Olivito [a,b,1], Libera Siciliano [a,b,1], Maria Leggio [a,b,*], Frank Van Overwalle [c]

[a] Department of Psychology, Sapienza University of Rome, Italy
[b] Ataxia Laboratory, IRCCS Santa Lucia Foundation, Rome, Italy
[c] Faculty of Psychology and Educational Sciences, Vrije Universiteit Brussel, Belgium

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ABSTRACT

Neuroimaging studies on healthy subjects described the causal effective connectivity of cerebellar-cerebral social mentalizing networks, revealing the presence of closed-loops. These studies estimated effective connectivity by applying Dynamic Causal Modeling on task-related fMRI data of healthy subjects performing mentalizing tasks. Thus far, few studies have applied Dynamic Causal Modeling to resting-state fMRI (rsfMRI) data to test the effective connectivity within the cerebellar-cerebral mentalizing network in the absence of experimental manipulations, and no study applied Dynamic Causal Modeling on fMRI data of patients with cerebellar disorders typically showing social cognition deficits. Thus, in this research we applied spectral Dynamic Causal Modeling, to rsfMRI data of 13 patients affected by spinocerebellar ataxia type 2 (SCA2) and of 23 matched healthy subjects. Specifically, effective connectivity was tested between acknowledged mentalizing regions of interest: bilateral cerebellar Crus II, dorsal and ventral medial prefrontal cortex, bilateral temporo-parietal junctions and precuneus. SCA2 and healthy subjects shared some similarities in cerebellar-cerebral mentalizing effective connectivity at rest, confirming the presence of closed-loops between cerebellar and cerebral mentalizing regions in both groups. However, relative to healthy subjects, SCA2 patients showed effective connectivity variations mostly in cerebellar-cerebral closed loops, namely weakened inhibitory connectivity from the cerebellum to the cerebral cortex, but stronger inhibitory connectivity from the cerebral cortex to the cerebellum. The present study demonstrated that effective connectivity changes affect a function-specific mentalizing network in SCA2 patients, allowing to deepen the direction and strength of the causal effective connectivity mechanisms driven by the cerebellar damage associated with SCA2.

1. Introduction

SCA2 is a rare autosomal dominant inherited cerebellar neurodegenerative disease due to the presence of expanded CAG trinucleotide repeats (≥32 CAG) in the gene encoding ataxin-2 (Pulst et al., 1996), characterized by extensive gray matter loss in the cerebellar cortex and by primary motor deficits (Auburger, n.d.; Della Nave et al., 2008; Estrada et al., 1999). Over the last decades, an extensive literature has provided evidence that SCA2 is also associated with a wide range of impairments in higher-order functions also including complex social cognitive functions (Clausi et al., 2021a; Lupo et al., 2018; Moriarty et al., 2016; Sokolovsky et al., 2010). Generally speaking, studies conducted on patients affected by cerebellar neurodegenerative disorders have provided general agreement on cerebellar participation to higher order social functions, showing the presence of deficits in different subcomponents of social cognitive domains, such as emotion and belief recognition, prediction of intentions, social judgements, and mentalizing or theory of mind (Clausi et al., 2021a, 2019; D'Agata et al., 2011; Olivito et al., 2023; Sokolovsky et al., 2010; Tamaš et al., 2021). Altogether, these studies suggest that alterations in these specific domains are due to structural damage confined to the Crus I-II and to changes in the functional flow of information between these cerebellar lobules and regions of the social brain, such as the precuneus, the medial prefrontal cortex (mPFC), and the temporo-parietal junction (TPJ) (Clausi et al., 2019; Olivito et al., 2023). With respect to studies in SCA2, in-depth analyses of neurobiological underpinnings of mentalizing deficits in

* Corresponding author at: Department of Psychology, Sapienza University of Rome, Italy.
E-mail address: maria.leggio@uniroma1.it (M. Leggio).
[1] Shared first authorship.

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this population of patients have provided additional insight into understanding cerebellar-cerebral mentalizing networks (Clausi et al., 2021a; Olivito et al., 2020). An anatomo-functional study found significant correlations between social cognition alterations and structural damage to the right Crus II and microstructural alterations in the cerebellar peduncles (Clausi et al., 2021a). Consistently, a resting-state functional MRI (rsfMRI) study reported altered inter-nodal functional connectivity between the right Crus II and mentalizing areas of the default-mode network (DMN), namely the dorsomedial prefrontal cortex (dmPFC) and the TPJ (Olivito et al., 2020). According to this evidence, the social impairments in SCA2 are assumed to be induced by an aberrant cerebellar modulatory activity on key social cerebral areas, determining altered cerebellar-cerebral loops (Clausi et al., 2021a; Olivito et al., 2020).

Considerable support to these hypotheses has also come from rsfMRI studies on healthy subjects (HS), which have largely established the characterization of the cerebellar functional topography for social processing and demonstrated that the cerebellum modulates all main large-scale functional brain networks, including the DMN (Alahmadi, 2023; Bostan et al., 2018; Buckner et al., 2011; Van Overwalle et al., 2019). In the history of social mentalizing, the DMN has gained wider attention since it integrates a body of regions in the cerebral cortex that are essential for social understanding and reasoning about others' mental states, such as TPJ, precuneus, posterior cingulate cortex, ventromedial prefrontal cortex (vmPFC), dmPFC, and superior frontal gyrus (Raichle et al., 1996; Schilbach et al., 2008). Both task-related fMRI (trfMRI) and rsfMRI studies in HS have shown that specific areas in the posterior cerebellum, the bilateral Crus II, are coupled to areas belonging to the DMN (Bostan et al., 2018; Pu et al., 2023; Stoodley et al., 2012; Stoodley and Schmahmann, 2018; Van Overwalle et al., 2019).

In a *meta*-analysis of trfMRI studies on HS applying a psychophysiological interaction (PPI) analysis, Van Overwalle and Mariën (2016) revealed the presence of functional connections (FC) in a cerebellar-cerebral mentalizing network, including the cerebellar Crus II and regions of the DMN, such as the bilateral TPJ, precuneus, and mPFC. This network was mainly activated when participants were required to reason about complex states of mind of others (Van Overwalle and Mariën, 2016). However, a PPI analysis is limited in that it does not permit interpretations about causality and directionality of the cerebellar-cerebral connections. To overcome these limitations, in a follow-up study, the same authors estimated the effective connectivity (EC) by employing a more advanced fMRI connectivity analysis named Dynamic Causal Modeling (DCM) which does allow to estimate the direct or "effective" connection between areas (without indirect interference from other connections) as well as their twofold directionality (Van Overwalle et al., 2019). Specifically, the DCM was applied to the same trfMRI data of the previous study allowing to discover bidirectional effective connections between the right Crus II and the bilateral TPJ, demonstrating that those cerebellar and cerebral mentalizing regions were effectively connected via closed loops (Van Overwalle et al., 2019). Generally, closed loops are defined as connections that send signals from an area of the cerebral cortex to a region of the cerebellum and receive feedback from that same cerebellar region. In this context, a recent DCM study aiming at exploring the trfMRI EC of the cerebellum with the cerebrum in processing social action sequences, confirmed the previous findings detecting many significant closed loops between the Crus I/II and cerebral mentalizing (e.g., dmPFC) and executive control areas (e.g., medial and lateral prefrontal cortices) (Pu et al., 2023).

TrfMRI and rsfMRI studies have greatly supported each other in characterizing the cerebellar-cerebral mentalizing networks. rsfMRI data analysis has been employed to explore the integration of specialized functional regions in the brain, via both FC and EC. While FC estimates the functional association between spatially distant areas in the brain, EC computes the stream of information by inferring the causal influence a given brain region exerts on another. Lately, a specific DCM – referred to as spDCM – was implemented to infer EC in rsfMRI (Friston et al., 2014). spDCM is adopted to model the intrinsic dynamics of a resting-state network and to make detailed inferences on the interplay between latent neural states at rest (Razi et al., 2015). The resulting EC patterns provide the directionality of the propagation of information within functional networks and the strength of the reciprocal connectivity (Almgren et al., 2018; Razi et al., 2015). Generally speaking, the investigation of intrinsic resting-state brain dynamics provides an important, ecologically valid perspective on brain function and mental life. While numerous FC studies supported the contribution of the Crus I/II in intrinsic connectivity networks associated with social mentalizing (Bostan et al., 2018; Buckner et al., 2011; Habas et al., 2009), to the best of our knowledge only one study has been recently conducted that specifically investigated cerebellar-cerebral EC at rest in healthy subjects (Bukhari et al., 2022). Bukhari and colleagues (Bukhari et al., 2022) applied DCM to rsfMRI data of HS taking into account cerebellar and cerebral default mode, attentional, and motor networks (Bukhari et al., 2022). They found mostly uniform and bidirectional interactions in the considered networks, reporting that domain-specific functional networks in the cerebellum are mutually connected to domain-specific functional networks in the cerebral cortex (Bukhari et al., 2022). All this evidence supports the hypothesis that the altered cerebellar functional modulation of cerebral projection areas involved in emotional and mentalizing processing (Clausi et al., 2021a; Olivito et al., 2020) could underlie the social cognition difficulties reported in SCA2 patients who present structural or functional alterations in the cerebellum. However, according to the anatomical (Kelly and Strick, 2003) and functional (Van Overwalle et al., 2019) organization of the cerebellum, to infer the direction and strength of FC changes within cerebello-cerebral network may be crucial to better clarify the neuropathological mechanisms underlying patients social symptoms. Indeed, through the closed loops, the social information, is propagated from the cerebrum to an internal model in the cerebellum which sends back error signals that are used by the cerebral cortex to adjust its activation in the opposite direction (Van Overwalle et al., 2019).

All in all, thus far, rsfMRI studies on SCA2 have mainly focused on the functional association between spatially distant areas in the brain, but they do not allow to infer causal interactions within these regions, providing crucial but still opening findings. The present study aims to fill this gap by extending our previous investigations of cerebellar-cerebral functional alterations in SCA2 patients (see Olivito et al., 2020; Clausi et al., 2021a), by detangling causal directionalities within the connectivity and further uncover neuropathological mechanisms underlying this condition.

Therefore, here we used fMRI data of SCA2 patients previously acquired for the above mentioned studies in order to estimate EC at rest using spDCM (Friston et al., 2014; Razi et al., 2015). This approach allows us to investigate the complex EC patterns in the cerebellar-cerebral mentalizing closed-loops while also estimating the connectivity within the cerebellum and cerebrum, thus inferring the causal influence that one region exerts over another. The regions of interests were chosen based on the mentalizing network described in the trfMRI DCM study of Van Overwalle and colleagues (Van Overwalle et al., 2019) and included the bilateral Crus II, the bilateral TPJ, the precuneus, the vmPFC and dmPFC. The Parametric Empirical Bayes (PEB (Friston et al., 2016)) module of DCM was applied to estimate EC differences between SCA2 patients and a group of age matched HS. We focused on common and distinct patterns of EC between SCA2 patients and HS. Consistent with Van Overwalle and colleagues (Van Overwalle et al., 2019), we expected to find substantial closed-loops in the mentalizing cerebellar-cerebral network in both groups, with specific changes occurring in the functional closed-loop connectivity of SCA2 patients.

2. Materials and methods

2.1. Participants

For the present study, retrospective data of 13 patients with a genetic diagnosis of SCA2 [female/male: 7/6; mean age/SD at the time of the clinical and magnetic resonance imaging (MRI) assessment: 47.5/8.6 (years)] were selected from a database of patients admitted to the Ataxia Laboratory of the IRCCS Santa Lucia Foundation from 2016 to 2019. All patients received their diagnosis at least 6 months prior to scanning and showed no other neurological signs except for CB4, who presented the Babinski sign. An expert neurologist examined the patients to confirm the presence of pure cerebellar motor symptoms and assessed the severity of their ataxia-related motor symptoms using the International Cooperative Ataxia Rating Scale (ICARS) (Trouillas et al., n.d.). The inclusion of patients was ensured when no history of extracerebellar neurologic pathology or psychiatric disorders was reported. Demographic characteristics and clinical scores of the SCA2 group are summarized in Table 1.

As control group, 23 HS with no history of neurological or psychiatric illness [female/male: 17/6; mean age/SD: 52.4/6.38)] were selected from a retrospective MRI database collected from 2016 to 2019 at the Neuroimaging Laboratory of the IRCCS Santa Lucia Foundation. The sample size was consistent with a previous resting-state fMRI study comparing SCA2 patients and HS (Olivito et al., 2020). No significant differences were found between SCA2 patients and HS in age or sex distribution as assessed by the *t*-test ($t = 1{,}93$; $p = 0.06$) and chi-square (X^2) analysis ($X^2 = 1{,}50$; $p = 0.21$), respectively.

Data used partially overlapped with the samples of other studies (Clausi et al., 2021a; Olivito et al., 2020, 2017).

The Ethics Committee of the Santa Lucia Foundation approved this study (CE/PROG.570), which was performed in accordance with the principles expressed in the Declaration of Helsinki. Written informed consent was obtained from each participant.

2.2. MRI data acquisition

The data were acquired on a 3.0-T (Achieva, Philips) scanner. Resting-state functional images were obtained using an echo-planar imaging sequence (EPI) sensitized to blood oxygenation-level dependent imaging (BOLD) contrast (TR 2080 ms, TE 30 ms, 32 axial slices parallel to AC-PC line, matrix 64 × 64, pixel size 3 × 3 mm^2, slice thickness 2.5 mm, flip angle 70°). BOLD echo planar images were collected during rest for a 7-min and 20-s period, resulting in a total of 220 volumes. During the fMRI scans, subjects were instructed to keep their eyes closed, not to think of anything, and not to fall asleep. Additionally, the following conventional MRI scans were acquired: dual-echo turbo spin echo [TSE] (TR = 6190 ms, TE = 12/109 ms); (2) fast-FLAIR (TR = 8170 ms, 204TE = 96 ms, TI = 2100 ms); (3) T1-weighted 3D high-resolution scan (3D modified driven equilibrium Fourier transform (MDEFT) (TR = 1338 ms, TE = 2. 4 ms, mat r i x = 256 × 224 × 176, in- plane FOV = 250 × 250 mm2, slice thickness = 1 mm).

The TSE scans of patients, acquired as part of this research study, were reviewed by an expert neuroradiologist to characterize the brain anatomy and ensure the absence of any macroscopic structural abnormalities.

For the HS group, conventional MRI was inspected to exclude any pathological conditions according to the inclusion criteria.

Table 1
Clinical and demographic characteristics of the SCA2 patients.

ID	Age	Sex	Disease duration (months)	ICARS TOTAL SCORES	CAG repeats
CA1	42	F	12	47	22/39
CA2	42	F	13	28	14/47
CA3	54	F	12	27	22/37
CA4	36	F	8	37	22/42
CA5	65	M	36	27	22/35
CA6	44	F	12	28	n.a.
CA7	62	F	48	31	22/37
CA8	41	M	36	18	22/38
CA9	42	M	12	24	22/39
CA10	44	M	64	17	22/39
CA11	48	M	47	29	22/38
CA12	54	M	96	24	n.a.
CA13	44	F	118	61	n.a.
Means (SD)	47.5 (8.7)	7/6	39.5(35.2)	30.6(11.9)	–

F = Female; M = Male; ICARS = International Cooperative Ataxia Rating Scale – ICARS range: minimum score 0 (absence of motor deficits), maximum score 100 (maximum presence of motor deficits); n.a. (not available) = Genetic data are not available for patients CA6, CA12, CA13 because at the time of their diagnosis, genetic testing did not include determination of the number of triplet repeats; SD = Standard deviation. Disease duration corresponds to the time from the genetic testing.

2.3. Resting-state fMRI data preprocessing

rsfMRI data were previously pre-processed using Statistical Parametric Mapping version 8 [Wellcome Department of Imaging Neuroscience; SPM8 (https://www.fil.ion.ucl.ac.uk/spm/), and in-house software implemented in Matlab (The Mathworks Inc., Natick, Massachussetts, USA). For each subject, the first four volumes of the fMRI series were discarded to allow for T1 equilibration effects. The preprocessing steps included correction for head motion, compensation for slice-dependent time shifts, normalization to the EPI template in MNI coordinates provided with SPM8 and smoothing with a 3D Gaussian Kernel with 8 mm^3 full width at half maximum. For each data set, motion correction was checked to ensure that the maximum absolute shift did not exceed 2 mm and the maximum absolute rotation did not exceed 1.5°. The global temporal drift was removed using a third-order polynomial fit, and the signal was regressed against the realignment parameters, and the signal averaged over whole brain voxels, to remove other potential sources of bias. Then, all images were filtered by a phase-insensitive band-pass filter (pass band 0.01–0.08 Hz) to reduce the effect of low-frequency drift and high-frequency physiological noise. Every participant's MDEFT was segmented in SPM and the total grey matter (GM) volume was estimated for SCA2 (mean/SD: 645.9/52.5) and HS (mean/SD: 659.2/45.9) participants. As assessed by the *t*-test analysis, no significant differences were found in the total GM volume between the two groups ($t = 0.03$; $p = 0.97$).

2.4. Spectral dynamic causal modeling

To study the EC of SCA2 patients and controls, we used the spDCM method on resting state fMRI.

To apply DCM, regions of interest (ROIs) were chosen according to the multi-study DCM analysis of Van Overwalle and colleagues (Van Overwalle et al., 2019) investigating cerebellar-cerebral EC in healthy subjects during social mentalizing tasks and which represented core mentalizing areas. The cerebral ROIs were centered around the mean MNI coordinates and included the dmPFC (with center at 0 50 35), vmPFC (0 50 5), right (R) and left (L) TPJ (±50 – 55 25), and precuneus (0 – 60 40) while the cerebellar ROI involved R and L Crus II (±25 – 75 – 40). ROIs were created by extracting the time series using the eigenvariate within a sphere with a radius of 15 mm around the center of the ROIs for the cerebrum, and of 8 mm for the cerebellum given its smaller size (and of its mentalizing network).

The optimal DCM across all participants was estimated according to the procedures described in Friston et al. (2016), Razi et al. (2015), Zhou et al. (2018) and detailed in Van Overwalle et al. (2019).

SPM12 was used to specify and estimate a full DCM for each participant. A full model allows all connectivity parameters in all directions to be freely estimated. We specified a bilinear deterministic

DCM without centering around the mean (Friston et al., 2003), which included all forward and backward connections between the ROIs. Note that the connections in DCM correspond to rate constants and are expressed in units of 1/s (i.e., of hertz). A DCM model was estimated for all participants using the same procedures for each sample.

A PEB model was then constructed for the whole group of participants over all parameters. This allowed to estimate the EC averaged across all participants taking into account the within-participants variability on the connectivity parameters, thus modelling the commonalities across the two groups. To know how the connectivity of SCA2 patients differs from controls, a covariate was then introduced which contrasted patients from controls, by setting weights of +1 and −1 for SCA2 and HS, respectively. Consequently, higher values of the covariates indicate that patients have higher EC than controls.

Next, a Bayesian model reduction (BMR) was used to remove redundant ECs and search over PEB models with different combinations of connections and group differences (Zhou et al., 2018). Specifically, BMR pruned away any connectivity parameter from the group-level PEB that did not contribute to the model evidence (Friston et al., 2016). A greedy search iteratively prunes connection parameters from the full model until the model evidence starts to decrease, so that the most relevant nested models from the full PEB model are tested. Bayesian model averaging of the parameters of the best 256 pruned models was applied and used for group inferences (Zhou et al., 2018), determining the winning model empirically.

Group-level analyses were then performed using Bayesian posterior inference, which is the Bayesian posterior probability (Bayesian-PP) of the model with a given parameter switched on or off. The advantage of thresholding using this approach is that the full covariance of the parameters is considered when computing a difference (Zeidman et al., 2019). Consequently, Bayesian-PP indicates the confidence in whether the mean of an EC within a group is different from zero or the confidence in the degree of linear relationship between variables. As suggested by Zeidman et al. (2019), connectivity parameters were considered to be significant when their posterior probability $p > 0.95$ (Van Overwalle et al., 2019). Additionally, a Spearman's correlation analysis was performed to investigate whether ECs patterns in SCA2 patients were associated to disease duration and ICARS motor scores.

3. Results

Our main interest regarded commonalities and differences between SCA2 patients and HS group in terms of cerebellar-cerebral closed loop. Fig. 1A shows the common pattern of EC evidenced in the two groups (Bayesian-PP > 0.95). Consistent with Van Overwalle et al. (2019), we found bidirectional connections (i.e., closed loops) between the social cerebellar ROI and key mentalizing cerebral ROI (Fig. 1B). Most closed loops connected the cerebellum with both ipsilateral and contralateral cerebral areas and vice versa.

It is of interest to note that all the significant upward connections coming from the cerebellum to the cerebral cortex were negative, whereas downward connections going toward the cerebellum were both positive and negative (see commonalities in Table 2). Connections between areas within the cerebral cortex were both positive and negative (see Table 3).

Specifically, as shown in the commonalities in Table 2, negative connections were found from the L-Crus II to precuneus, bilateral TPJ, vmPFC and dmPFC as well as from the R-Crus II to precuneus, L-TPJ and vmPFC. The connections entering the L-Crus II included positive influences from the precuneus and dmPFC, and negative influences from the bilateral TPJ and vmPFC. Finally, connections entering the R-Crus II were positive from the precuneus and negative from the L-TPJ and vmPFC.

Table 2
EC commonalities and differences in cerebellar-cerebral closed loops between SCA2 and HS.

Closed loops		Commonalities (SCA2 & HS)	Differences (SCA2 > HS)	HS	SCA2
From	**To**	**EC (Hz)**	**EC (Hz)**	**EC (Hz)**	**EC (Hz)**
L-Crus II	Precuneus	−0.20	0.19	−0.38	0.00
	L-TPJ	−0.18	–	–	–
	R-TPJ	−0.19	–	–	–
	vmPFC	−0.27	0.16	−0.40	−0.08
	dmPFC	−0.12	–	–	–
R-Crus II	Precuneus	−0.45	–	–	–
	R-TPJ	−0.28	0.12	−0.38	−0.13
	vmPFC	−0.43	0.28	−0.67	−0.18
Precuneus	L-Crus II	0.20	0.06	0.12	0.29
	R-Crus II	0.19	–	–	–
L-TPJ	L-Crus II	−0.16	–	–	–
R-TPJ	L-Crus II	−0.19	–	–	–
	R-Crus II	−0.16	−0.17	0.00	−0.28
vmPFC	L-Crus II	−0.20	−0.23	0.00	−0.42
	R-Crus II	−0.22	−0.24	0.01	−0.38
dmPFC	L-Crus II	0.13	–	–	–

EC = effective connectivity; L = left; R = right; TPJ = temporo-parietal junction, d/vmPFC = dorsal/ventral medial prefrontal cortex. In this table, all Bayesian-PP = 1.00 except for absolute values < 0.01. Absolute EC values of the pairwise regions showing differences between groups are also reported for HS and SCA2 separately. Commonalities and differences in unidirectional connections can be found in Supplemental Tables 1 and 2, respectively. Full EC patterns in HS and SCA2 are reported in Supplemental Tables 3 and 4, respectively.

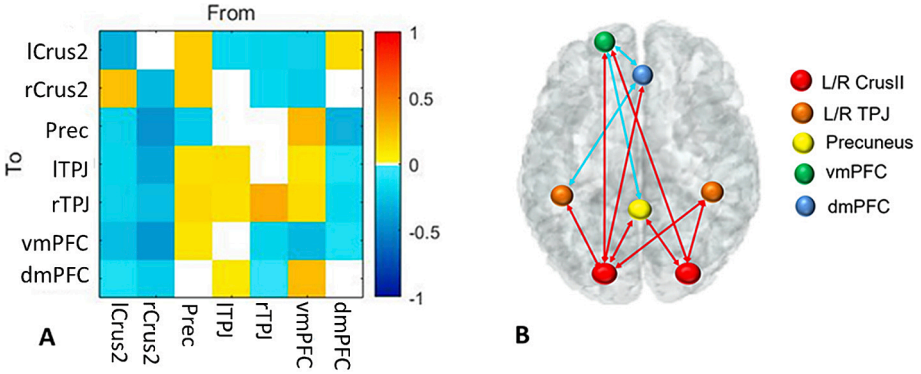

Fig. 1. Mean values in effective connectivity for SCA2 patients and HS. (A) Commonalities in effective connectivity in the patients and HS. (B) Common pattern of bidirectional cerebellar-cerebral (red arrows) and cerebro-cerebral ECs (cyan arrows) in SCA2 and HS. Left and right side are reported in neurological convention. L = left; R = right; TPJ = temporo-parietal junction; vmPFC = ventromedial prefrontal cortex; dmPFC = dorsomedial prefrontal cortex. For reasons of visibility, the vmPFC which is located at x = 0 was depicted slightly to the left. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 3
EC commonalities in within-cerebral closed loops between SCA2 and HS.

Closed loops		Commonalities
From	**To**	**EC (Hz)**
Precuneus	vmPFC	0.10
L-TPJ	dmPFC	0.08
R-TPJ	vmPFC	−0.18
	dmPFC	−0.07
vmPFC	Precuneus	0.28
	R-TPJ	0.13
	dmPFC	0.25
dmPFC	L-TPJ	−0.11
	R-TPJ	−0.17
	vmPFC	−0.12

EC = effective connectivity; L = left; R = right; TPJ = temporo-parietal junction, d/vmPFC = dorsal/ventral medial prefrontal cortex. In this table, all Bayesian-PP = 1.00. There are no differences of closed loops within the cerebrum. Commonalities and differences in unidirectional connections can be found in Supplemental Tables 1 and 2, respectively. Full EC patterns in HS and SCA2 are reported in Supplemental Tables 3 and 4, respectively.

Bidirectional within-cerebral ECs were also found (Table 3). In particular, positive connections were observed from the precuneus to vmPFC, from the L-TPJ to dmPFC, from the vmPFC to precuneus, R-TPJ and dmPFC, while negative connections were found from R-TPJ to vmPFC and dmPFC, from the dmPFC to L-TPJ, R-TPJ and vmPFC. A full description of EC commonalities is reported in Supplemental Table 1.

Different effective connections between the two groups are shown in Fig. 2A (Bayesian-PP > 0.95). Group differences in the closed loops are depicted in Fig. 2B and their directionality is listed in Table 2 (SCA2 > HS). Absolute EC values of the pairwise regions showing differences between groups are also reported for HS and SCA2 separately. Compared to HS, SCA2 showed weakened negative cerebellar-cerebral ECs from L-Crus II to precuneus and vmPFC, and from R-Crus II to R-TPJ and vmPFC. Conversely, stronger positive cerebro-cerebellar ECs were found from the precuneus to L-Crus II, while stronger negative cerebro-cerebellar ECs were found from R-TPJ to R-Crus II and from vmPFC to L-Crus II and R-Crus II (see differences in Table 2). No significant ECs differences were found in cerebro-cerebral closed loops.

A full description of EC differences is reported in Supplemental Table 2. Results of correlational analysis between significant cerebellar-cerebral ECs patterns and disease duration and ICARS motor scores are reported in Supplemental Table 5.

4. Discussion

In the present study, DCM was used to investigate resting-state EC between mentalizing areas of the cerebellum and mentalizing areas located in the cerebrum in the presence of a cerebellar pathological condition, i.e., SCA2. The aim was to provide data on the physiopathological mechanism subtending social cognition alterations observed in SCA2 patients. Interestingly, our findings revealed effective changes in the strength of cerebellar-cerebral mentalizing closed loops in SCA2. The main findings evidenced weakened negative ECs from the bilateral Crus II to mentalizing cerebral regions (i.e., precuneus, vmPFC and right TPJ) while stronger negative ECs were found from the same mentalizing cerebral regions to bilateral Crus II.

The contribution of Crus I/II in intrinsic connectivity networks associated with social mentalizing has been supported by numerous FC studies indicating a cerebellar functional segregation for social processing such that the mentalizing network in the cerebellum is functionally connected with the mentalizing network of the cerebrum, which mainly consists of areas of the DMN in both brain structures (Bostan et al., 2018; Buckner et al., 2011; Habas et al., 2009; Krienen and Buckner, 2009).

While the investigation of intrinsic resting-state brain dynamics may provide an important insight into understanding brain function, the investigation of EC by means of DCM has many advantages over traditional FC. Indeed, the DCM approach allows to define causal effects by analyzing whether the preceding neural activity in one seed region predicts activity in another subsequent region, providing information about directed or causal interactions underlying the observed correlations (Friston et al., 2003). Thus, the integration within a neural system is better understood when investigating EC since it reflects the influence of one neural system over another one (Friston et al., 2014).

DCM was originally developed to estimate EC for task related fMRI studies (Friston et al., 2003). In the context of cerebellar research, a recent DCM study exploring task related cerebellar-cerebral EC in HS detected many significant closed loops between Crus I/II and cerebral mentalizing (e.g., dmPFC) (Van Overwalle et al., 2019).

The presence of closed loops between the cerebellar Crus I/II and key social brain regions (i.e., bilateral TPJ, precuneus, and dmPFC) represent the neural substrate subtending the crucial cerebellar role in social cognition (Van Overwalle et al., 2019; Van Overwalle and Mariën, 2016). Specifically, it has been proposed that the cerebellum produces internal models of mental processes that occur during social interactions in which the prediction of sequential events is crucial (Leggio and Molinari, 2015). Through this mechanism the cerebellum may modulate cerebral activity and promote optimized feedforward control required to turn social interactions into fluid and automatic behaviors and to rapidly adapt to new social patterns when novelty is met. When discrepancies occur between the predicted sequences of social events and the ongoing social interaction, the cerebellum sends alert signals to widespread

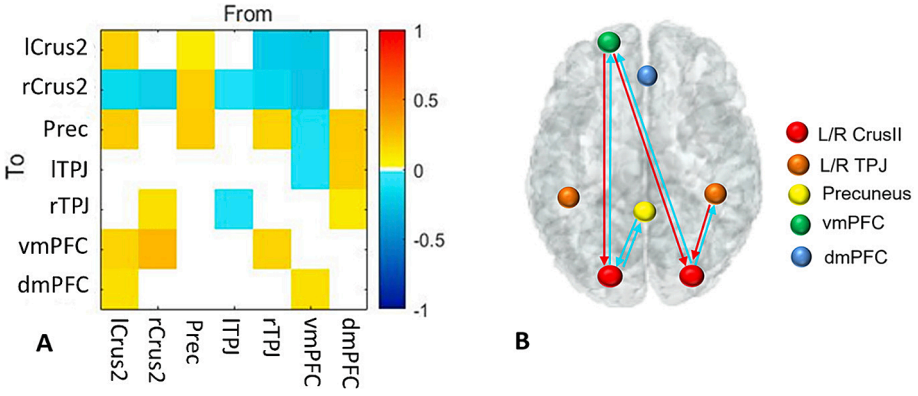

Fig. 2. Group difference between SCA2 patients and HS. (A) Differences in ECs of patients and HS. (B) Stronger negative (red arrows) and weakened negative/stronger positive (cyan arrows) connections in SCA2 patients compared to HS. Left and right side are reported in neurological convention. L = left; R = right; TPJ = temporo-parietal junction; vmPFC = ventromedial prefrontal cortex; dmPFC = dorsomedial prefrontal cortex. For reasons of visibility, the vmPFC which is located at x = 0 was depicted slightly to the left. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

regions in the social brain to warn about the need for error correction (Leggio and Molinari, 2015). Thus, if cerebellar structural alterations occur, this would impair cerebellar error checking, interfering with the modulatory function of the cerebellum on the cortical projection areas involved in the social process so that social behavior is not always appropriately adjusted to specific social environmental requirements (Clausi et al., 2021b; Olivito et al., 2023; Van Overwalle et al., 2020).

Interestingly, it has been suggested previously that neuroanatomical damage in Crus II may alter cerebellar-cerebral mentalizing networks in SCA2 (Clausi et al., 2021a; Olivito et al., 2020) accounting for patients' social impairments. rsfMRI studies also provided important insight into understanding the neural substrate subtending social dysfunction in SCA2 patients (Olivito et al., 2020). Consistently, these studies showed changes in the functional flow of information between key cerebellar lobules and social brain regions, such as the precuneus, PFC, and TPJ (Clausi et al., 2019; Olivito et al., 2023). However, none of these studies provided information about how the neural-signal flow within the mentalizing cerebellar-cerebral network is changed in SCA2 patients. Considering the anatomical (Kelly and Strick, 2003) and functional (Van Overwalle et al., 2019) evidence of cerebellar-cerebral closed loops, investigating the direct influence of the cerebellum on mentalizing cerebral regions and vice versa is particularly important to provide detailed information about physiopathological mechanisms in SCA2. In this framework, detailed inferences on the mutual interplay between latent neural states (Razi et al., 2015) can be derived by applying DCM to a resting-state network. Importantly, this is the first study using the DCM approach to investigate mentalizing cerebellar-cerebral closed loops at rest in cerebellar patients affected by SCA2.

Consistent with the findings of Van Overwalle et al. (2019), the present connectivity data also support the existence of cerebellar-cerebral mentalizing closed loops at rest. In particular, the common EC pattern between SCA2 and HS evidenced that all the connections coming from the cerebellum to cerebral cortex are negative (i.e., inhibitory), which might suggest that the cerebellum sends out negative error signals. Interestingly, the resting-state pattern of cerebellar connections involves mentalizing cerebral regions that were not detected in the trfMRI DCM study of Van Overwalle et al. (2019), that is, no direct connections were found between the cerebellum and the mPFC (see also Ma et al., 2023) but were found in another study by Pu et al. (2023). This may suggest that some coupled fluctuations within cerebellar-cerebral networks may be suppressed during some tasks and become more pronounced during other tasks as well as rest. Indeed, a very interesting aspect of rsfMRI is that the signals that are sometimes discarded in trfMRI studies are taken into consideration as they reflect fluctuations in unlimited, spontaneous thought (Fox and Greicius, 2010).

The pattern of common connections between SCA2 and HS at rest is also consistent with the anatomical evidence of cerebellar-cerebral closed loops (Kelly and Strick, 2003; Suzuki et al., 2012). Specifically, the contralateral connectivity from the left Crus II to the right TPJ is consistent with earlier anatomical evidence showing a preference for contralateral connectivity (Kelly and Strick, 2003). In contrast, the ipsilateral connectivity between the left Crus II and left TPJ (as well as the right Crus II and right TPJ) is in line with both anatomical and functional research showing that a minority of connections terminate in ipsilateral cerebral areas (Krienen and Buckner, 2009; Salmi et al., 2010; Sokolov et al., 2014; Suzuki et al., 2012).

Thus, through these closed loops, social information is propagated from the cerebrum to an internal model in the cerebellum which sends back error signals that are used by the cerebral cortex to adjust its activation in the opposite direction (Van Overwalle et al., 2019). It has to be mentioned that connections entering the cerebellum are both positive (i.e., excitatory) and negative (i.e., inhibitory). In particular, in line with task-related DCM results in HS (Van Overwalle et al., 2019), we found excitatory influence from the precuneus to bilateral Crus II. Differently, inhibitory influences have been found from the TPJ and vmPFC, suggesting that these regions may have suppressive influence on the cerebellum at rest.

Interestingly, the comparison between patients and HS evidenced a weakened negative upward cerebellar-cerebral EC in SCA2. Since all the connections from the cerebellum towards cerebral cortex were negative, this finding suggests a weaker pattern of inhibition exerted by the cerebellum on connected cerebral cortex regions. In the opposite direction, most downward connections entering the cerebellum from the cerebral cortex showed stronger negative EC in SCA2, suggesting an opposite trend of a stronger pattern of inhibition exerted by the cerebrum on cerebellar regions.

Thus, in presence of a cerebellar pathology, internal sequencing prediction of the cerebellum based on the input of the cerebrum may be altered leading to an aberrant cerebellar modulatory activity when matching social information with current social behavior. We speculate that the weakened cerebellar inhibition exerted on social cerebral regions results in abnormal error monitoring and inappropriate response to cerebral social inputs leading to maladaptive behavioral corrections. According to these findings, social impairments observed in SCA2 may be assumed to be driven by neural loss in cerebellar Crus II reported in these patients (see Clausi et al., 2021a), that in turn induce imbalanced interaction between key cerebellar and cerebral regions involved in social functions, determining altered cerebellar-cerebral loops (Clausi et al., 2021a; Olivito et al., 2020).

There are some limitations in our current study. First, although this research elucidates the causal pattern of alterations within cerebellar-cerebral closed loops in the presence of a cerebellar pathology, these findings need to be replicated with larger or independent patient populations. Nevertheless, it has to be considered that the strict inclusion criteria and the fact that SCA2 is considered a rare disease with specific genetic roots clearly affected the recruitment rate. Second, in the present study, correlations between the altered pattern of cerebellar-cerebral EC and social performances of SCA2 was not investigated, preventing from making direct causal inferences. Nevertheless, although it is known that the Crus II is also involved in other higher-order functions including visuospatial and executive abilities (Leggio and Olivito, 2018), our hypothesis is supported by a previous study of our group in which we found a positive correlation between the GM volume of Crus 2 and the SC performances in the same SCA2 group (Clausi et al., 2021a). Third, the present evidence does not allow to make inferences about the specific mechanism subtending altered cerebellar prediction processing, that is, whether cerebellar generated internal models are disrupted or cannot be properly accessed for anticipating future events. Considering all these observations, further efforts are required to overcome these limitations and draw valid conclusions on the impact of the EC on social impairments observed in patients with SCA2.

In spite of these limitations, the present dynamic modeling analysis provides the first characterization of resting-state cerebellar-cerebral EC in SCA2, further supporting the recently acknowledged critical role of the cerebellum in social mentalizing. Although future research will be needed in order to explore open questions and further support the present conclusions, this study could be particularly important towards a better comprehension of the neurobiological substrates of social difficulties experienced by cerebellar patients and the identification of MRI patterns that may serve as reliable disease biomarkers. These aspects should be considered when a therapeutic approach is applied since they allows to track disease progression and the longitudinal effect of rehabilitation on the identified network. Hence, this could pave the way for the implementation and development of specific rehabilitation protocols that modulate cerebellar excitability (i.e., transcranial magnetic stimulation and direct current stimulation applied over the cerebellum), allowing clinicians to influence/improve symptomatology in individuals suffering from changes in different functional domains, including mentalization.

5. Conclusion

The present DCM study supports the existence of domain-specific mentalizing closed loops between the cerebellum and the cerebrum at rest. Most importantly, it demonstrates for the first time that specific cerebellar-cerebral EC alterations are associated with cerebellar neurodegenerative conditions, specifically SCA2, affecting cerebellar modulation on connected cerebral cortex regions. Although future research will be needed in order to explore open questions and further support the present conclusions, this study sheds more light on the putative neural substrate and underlying mechanisms of social dysfunction in SCA2 patients.

CRediT authorship contribution statement

Giusy Olivito: Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Libera Siciliano:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Maria Leggio:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Resources, Project administration, Funding acquisition, Data curation, Conceptualization. **Frank Van Overwalle:** Writing – review & editing, Supervision, Software, Resources, Methodology, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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References

Alahmadi, A.A.S., 2023. The cerebellum's orchestra: understanding the functional connectivity of its lobes and deep nuclei in coordination and integration of brain networks. Tomography 9, 883–893. https://doi.org/10.3390/tomography9020072.

Almgren, H., Van de Steen, F., Kühn, S., Razi, A., Friston, K., Marinazzo, D., 2018. Variability and reliability of effective connectivity within the core default mode network: a multi-site longitudinal spectral DCM study. Neuroimage 183, 757–768. https://doi.org/10.1016/j.neuroimage.2018.08.053.

Auburger, G.W.J., n.d. Spinocerebellar ataxia type 2 INTRODUCTION AND EPIDEMIOLOGY.

Bostan, A., Guell, X., Schmahmann, J.D., De Gabrieli, J., Ghosh, S.S., 2018. Functional gradients of the cerebellum. https://doi.org/10.7554/eLife.36652.001.

Buckner, R.L., Krienen, F.M., Castellanos, A., Diaz, J.C., Thomas Yeo, B.T., 2011. The organization of the human cerebellum estimated by intrinsic functional connectivity. J. Neurophysiol. 106, 2322–2345. https://doi.org/10.1152/jn.00339.2011.

Bukhari, Q., Ruf, S.F., Guell, X., Whitfield-Gabrieli, S., Anteraper, S., 2022. Interaction between cerebellum and cerebral cortex, evidence from dynamic causal modeling. Cerebellum 21, 225–233. https://doi.org/10.1007/s12311-021-01284-1.

Clausi, S., Olivito, G., Lupo, M., Siciliano, L., Bozzali, M., Leggio, M., 2019. The cerebellar predictions for social interactions: theory of mind abilities in patients with degenerative cerebellar atrophy. Front. Cell. Neurosci.. 12 https://doi.org/10.3389/fncel.2018.00510.

Clausi, S., Olivito, G., Siciliano, L., Lupo, M., Bozzali, M., Masciullo, M., Molinari, M., Romano, S., Leggio, M., 2021a. The neurobiological underpinning of the social cognition impairments in patients with spinocerebellar ataxia type 2. Cortex 138, 101–112. https://doi.org/10.1016/j.cortex.2020.12.027.

Clausi, S., Olivito, G., Siciliano, L., Lupo, M., Laghi, F., Baiocco, R., Leggio, M., 2021b. The cerebellum is linked to theory of mind alterations in autism. A direct clinical and MRI comparison between individuals with autism and cerebellar neurodegenerative pathologies. Autism Res. 14, 2300–2313. https://doi.org/10.1002/aur.2593.

D'Agata, F., Caroppo, P., Baudino, B., Caglio, M., Croce, M., Bergui, M., Tamietto, M., Mortara, P., Orsi, L., 2011. The recognition of facial emotions in spinocerebellar ataxia patients. Cerebellum 10, 600–610. https://doi.org/10.1007/s12311-011-0276-z.

Della Nave, R., Ginestroni, A., Tessa, C., Cosottini, M., Giannelli, M., Salvatore, E., Sartucci, F., De Michele, G., Dotti, M.T., Piacentini, S., Mascalchi, M., 2008. Brain structural damage in spinocerebellar ataxia type 2. A voxel-based morphometry study. Movement Disorders 23, 899–903. https://doi.org/10.1002/mds.21982.

Estrada, R., Galarraga, J., Orozco, G., Nodarse, A., Auburger, G., 1999. Spinocerebellar ataxia 2 (SCA2): morphometric analyses in 11 autopsies. Acta Neuropathol. 97, 306–310. https://doi.org/10.1007/s004010050989.

Fox, M.D., Greicius, M., 2010. Clinical applications of resting state functional connectivity. Front. Syst. Neurosci. https://doi.org/10.3389/fnsys.2010.00019.

Friston, K.J., Harrison, L., Penny, W., 2003. Dynamic causal modelling. Neuroimage 19, 1273–1302. https://doi.org/10.1016/S1053-8119(03)00202-7.

Friston, K.J., Kahan, J., Biswal, B., Razi, A., 2014. A DCM for resting state fMRI. Neuroimage 94, 396–407. https://doi.org/10.1016/j.neuroimage.2013.12.009.

Friston, K.J., Litvak, V., Oswal, A., Razi, A., Stephan, K.E., Van Wijk, B.C.M., Ziegler, G., Zeidman, P., 2016. Bayesian model reduction and empirical Bayes for group (DCM) studies. Neuroimage 128, 413–431. https://doi.org/10.1016/j.neuroimage.2015.11.015.

Habas, C., Kamdar, N., Nguyen, D., Prater, K., Beckmann, C.F., Menon, V., Greicius, M. D., 2009. Distinct cerebellar contributions to intrinsic connectivity networks. J. Neurosci. 29, 8586–8594. https://doi.org/10.1523/JNEUROSCI.1868-09.2009.

Kelly, R.M., Strick, P.L., 2003. Behavioral/systems/cognitive cerebellar loops with motor cortex and prefrontal cortex of a nonhuman primate. J. Neurosci. 23 (8432), 8444. https://doi.org/10.1523/JNEUROSCI.23-23-08432.2003.

Krienen, F.M., Buckner, R.L., 2009. Segregated fronto-cerebellar circuits revealed by intrinsic functional connectivity. Cereb. Cortex 19, 2485–2497. https://doi.org/10.1093/cercor/bhp135.

Leggio, M., Molinari, M., 2015. Cerebellar sequencing: a trick for predicting the future. Cerebellum. https://doi.org/10.1007/s12311-014-0616-x.

Leggio, M., Olivito, G., 2018. Topography of the cerebellum in relation to social brain regions and emotions. In: Handbook of Clinical Neurology. Elsevier B.V, pp. 71–84. https://doi.org/10.1016/B978-0-444-63956-1.00005-9.

Lupo, M., Olivito, G., Iacobacci, C., Clausi, S., Romano, S., Masciullo, M., Molinari, M., Cercignani, M., Bozzali, M., Leggio, M., 2018. The cerebellar topography of attention sub-components in spinocerebellar ataxia type 2. Cortex 108, 35–49. https://doi.org/10.1016/j.cortex.2018.07.011.

Ma, Q., Pu, M., Haihambo, N., Baetens, K., Heleven, E., Deroost, N., Baeken, C., Van Overwalle, F., 2023. Effective cerebello–cerebral connectivity during implicit and explicit social belief sequence learning using dynamic causal modeling. Soc. Cogn. Affect. Neurosci. 18 https://doi.org/10.1093/scan/nsac044.

Moriarty, A., Cook, A., Hunt, H., Adams, M.E., Cipolotti, L., Giunti, P., 2016. A longitudinal investigation into cognition and disease progression in spinocerebellar ataxia types 1, 2, 3, 6, and 7. Orphanet J. Rare Dis. 11 https://doi.org/10.1186/s13023-016-0447-6.

Olivito, G., Lupo, M., Iacobacci, C., Clausi, S., Romano, S., Masciullo, M., Molinari, M., Cercignani, M., Bozzali, M., Leggio, M., 2017. Microstructural MRI basis of the cognitive functions in patients with spinocerebellar ataxia type 2. Neuroscience 366, 44–53. https://doi.org/10.1016/j.neuroscience.2017.10.007.

Olivito, G., Siciliano, L., Clausi, S., Lupo, M., Romano, S., Masciullo, M., Molinari, M., Cercignani, M., Bozzali, M., Leggio, M., 2020. Functional changes of mentalizing network in SCA2 patients: novel insights into understanding the social cerebellum. Cerebellum 19, 235–242. https://doi.org/10.1007/s12311-019-01081-x.

Olivito, G., Siciliano, L., Clausi, S., Lupo, M., Baiocco, R., Gragnani, A., Saettoni, M., Delle Chiaie, R., Laghi, F., Leggio, M., 2023. The cerebellum gets social: evidence from an exploratory study of cerebellar, neurodevelopmental, and psychiatric disorders. Biomedicines 11. https://doi.org/10.3390/biomedicines11020309.

Pu, M., Ma, Q., Haihambo, N., Li, M., Baeken, C., Baetens, K., Deroost, N., Heleven, E., Van Overwalle, F., 2023. Dynamic causal modeling of cerebello-cerebral connectivity when sequencing trait-implying actions. Cereb. Cortex 33, 6366–6381. https://doi.org/10.1093/cercor/bhac510.

Pulst, S.-M., Nechiporuk, A., Nechiporuk, T., Gispert, S., Chen, X.-N., Lopes-Cendes, I., Pearlman, S., Starkman, S., Orozco-Diaz, G., Lunkes, A., DeJong, P., Rouleau, G.A., Auburger, G., Korenberg, J.R., Figueroa, C., Sahba, S., 1996. Moderate expansion of a normally biallelic trinucleotide repeat in spinocerebellar ataxia type 2. Nat. Genet. 14, 269–276. https://doi.org/10.1038/ng1196-269.

Raichle, M.E., Macleod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A., Shulman, G.L., 1996. A Default Mode of Brain Function. National Academy of Sciences.

Razi, A., Kahan, J., Rees, G., Friston, K.J., 2015. Construct validation of a DCM for resting state fMRI. Neuroimage 106, 1–14. https://doi.org/10.1016/j.neuroimage.2014.11.027.

Salmi, J., Pallesen, K.J., Neuvonen, T., Brattico, E., Korvenoja, A., Salonen, O., Carlson, S., 2010. Cognitive and motor loops of the human cerebro-cerebellar

system. J. Cogn. Neurosci. 22, 2663–2676. https://doi.org/10.1162/jocn.2009.21382.
Schilbach, L., Eickhoff, S.B., Rotarska-Jagiela, A., Fink, G.R., Vogeley, K., 2008. Minds at rest? Social cognition as the default mode of cognizing and its putative relationship to the "default system" of the brain. Conscious. Cogn. 17, 457–467. https://doi.org/10.1016/j.concog.2008.03.013.
Sokolov, A.A., Erb, M., Grodd, W., Pavlova, M.A., 2014. Structural loop between the cerebellum and the superior temporal sulcus: evidence from diffusion tensor imaging. Cereb. Cortex 24, 626–632. https://doi.org/10.1093/cercor/bhs346.
Sokolovsky, N., Cook, A., Hunt, H., Giunti, P., Cipolotti, L., 2010. A preliminary characterisation of cognition and social cognition in spinocerebellar ataxia types 2, 1, and 7. Behav. Neurol. 23, 17–29. https://doi.org/10.3233/BEN-2010-0270.
Stoodley, C.J., Schmahmann, J.D., 2018. Functional topography of the human cerebellum. In: Handbook of Clinical Neurology. Elsevier B.V, pp. 59–70. https://doi.org/10.1016/B978-0-444-63956-1.00004-7.
Stoodley, C.J., Valera, E.M., Schmahmann, J.D., 2012. Functional topography of the cerebellum for motor and cognitive tasks: an fMRI study. Neuroimage 59, 1560–1570. https://doi.org/10.1016/j.neuroimage.2011.08.065.
Suzuki, L., Coulon, P., Sabel-Goedknegt, E.H., Ruigrok, T.J.H., 2012. Organization of cerebral projections to identified cerebellar zones in the posterior cerebellum of the rat. J. Neurosci. 32, 10854–10869. https://doi.org/10.1523/JNEUROSCI.0857-12.2012.
Tamaš, O., Kostić, M., Kačar, A., Stefanova, E., Đokić, B.S., Stanisavljević, D., Milovanović, A., Đorđević, M., Glumbić, N., Dragašević-Mišković, N., 2021. Social cognition in patients with cerebellar neurodegenerative disorders. Front. Syst. Neurosci. 15 https://doi.org/10.3389/fnsys.2021.664223.
Trouillas, P., Takayanagi, T., Hallett, M., Currier, R.D., Subramony, S.H., Wessel, K., Bryer, A., Diener, H.C., Massaquoi, S., Gomez, C.M., Coutinho, P., Hamida, M.B., Campanella, G., Filla, A., Schut, L., Timann, D., Honnorat, J., Nighoghossian, N., Manyam, B., n.d. NEU SC InternationalCooperativeAtaxia Rating Scale for pharmacological assessmentof the cerebella syndrome.
Van Overwalle, F., Mariën, P., 2016. Functional connectivity between the cerebrum and cerebellum in social cognition: a multi-study analysis. Neuroimage 124, 248–255. https://doi.org/10.1016/j.neuroimage.2015.09.001.
Van Overwalle, F., Van de Steen, F., Mariën, P., 2019. Dynamic causal modeling of the effective connectivity between the cerebrum and cerebellum in social mentalizing across five studies. Cogn. Affect. Behav. Neurosci. 19, 211–223. https://doi.org/10.3758/s13415-018-00659-y.
Van Overwalle, F., Van de Steen, F., van Dun, K., Heleven, E., 2020. Connectivity between the cerebrum and cerebellum during social and non-social sequencing using dynamic causal modelling. Neuroimage 206. https://doi.org/10.1016/j.neuroimage.2019.116326.
Zeidman, P., Jafarian, A., Seghier, M.L., Litvak, V., Cagnan, H., Price, C.J., Friston, K.J., 2019. A guide to group effective connectivity analysis, part 2: Second level analysis with PEB. Neuroimage 200, 12–25. https://doi.org/10.1016/j.neuroimage.2019.06.032.
Zhou, Y., Zeidman, P., Wu, S., Razi, A., Chen, C., Yang, L., Zou, J., Wang, G., Wang, H., Friston, K.J., 2018. Altered intrinsic and extrinsic connectivity in schizophrenia. Neuroimage Clin. 17, 704–716. https://doi.org/10.1016/j.nicl.2017.12.006.