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RELATION BETWEEN MOTOR FUNCTION AND CEREBELLAR STRUCTURE IN PSYCHOSIS

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1. ABSTRACT

Introduction

Recent research suggests that psychotic disorders are linked to abnormalities in both the structure and function of the cerebellum. Motor dysfunction seems to be an intrinsic trait of psychosis, being present in individuals previous to diagnosis and naive to antipsychotics. Given the cerebellum's role in motor coordination, it raises questions about whether these changes contribute to the motor alterations seen in individuals with the disorder.

Material and Methods

To explore these ideas, we studied 19 patients diagnosed with schizophrenia, bipolar or schizoaffective disorder. We assessed neurological soft signs (NSS) in all eligible patients using the Neurological Evaluation Scale and magnetic resonance imaging (MRI) was used to measure cerebellar volumes. Additionally, antipsychotic medication was studied as a potential confounding variable. The pharmacological therapy data was collected during hospital admission or follow-ups at the time of the neurological evaluation and transformed into chlorpromazine equivalents.

Results

Our findings revealed that higher scores in the subsequent subgroups of NSS correlated with significantly smaller cortical cerebellar volumes for both hemispheres. However, we did not observe this relation between NSS and white matter cerebellar volume. We also did not find any associations between cerebellar gray matter volumes and antipsychotic treatment, or between cerebellar volumes and NSS total score.

Conclusions

These results lend support to the hypothesis implicating the cerebellum in psychosis and suggest that these alterations are linked to NSS, independently of antipsychotic treatment. Therefore, the cerebellum, and as this study shows, particularly the cerebellar cortex can be part of the pathological basis for NSS and subsequently of the psychopathology of this spectrum of disorders.

Keywords: psychosis, cerebellum, neurological soft signs, NSS, antipsychotics.

2. INTRODUCTION

Currently, the clinical definition of psychosis entails the presence of hallucinations and delusions, accompanied by impaired reality testing. In the context of schizophrenia specifically, it is characterized by the occurrence of at least one of these core features – hallucinations, delusions or disorganized speech – coupled with abnormal psychomotor behaviour, or negative symptoms, with a minimum count of two, for at least six months, including at least one month of active psychotic symptoms [1]. Nevertheless, it is becoming increasingly evident that with this definition there is a considerable heterogeneity among patients, prompting the idea of conceiving schizophrenia rather as a spectrum.

In traditional classification frameworks, schizophrenia spectrum, and bipolar disorders had been considered as separate psychopathological entities. Yet, mounting evidence now indicates that these heterogeneous conditions show significant physiopathological interconnections [2,3]. The pathogenesis of psychosis is not yet completely understood, but in it numerous factors have been implicated. For instance, the neurodevelopmental hypothesis is becoming increasingly accepted. According to it, psychosis is a result of diverse pathological processes that take place during brain development and commence years before disease onset, in which there is an influence of an interplay between genetics and environmental factors [4].

In line with this perspective, several prospective studies, aimed at identifying potential biomarkers of the disease, have reported that certain motor impairments in early development are noticeable among children who later develop schizophrenia, as well as in those who exhibit high-risk of psychosis due to, for instance, familial history [5,6]. The occurrence of these alterations in early stages suggests there might be a shared underlying neurodevelopmental mechanism responsible for both motor and psychotic symptoms.

NSS are the most well-known and prevalent of these abnormalities and have been detected in high-risk individuals by many researchers [7]. They encompass subclinical deviations in the sensory integration, motor coordination and sequencing of complex motor acts performance. Considered as markers of neurodevelopmental delay, NSS often show improvement during adolescence in normal subjects, but are observed to persist across various psychiatric disorders, most prominently in psychosis. To illustrate this, the occurrence of NSS among individuals with schizophrenia has been reported as high as 73% [8]. Furthermore, they have been reported to be significantly more common in first-degree relatives of diagnosed patients than in healthy subjects [9]. Research also suggests that NSS are not exclusive to schizophrenia but can be as well observed in other disorders within the psychotic spectrum,

particularly bipolar disorder [10]. Interestingly, NSS have also been reported to be more prevalent among those with early onset schizophrenia – childhood-onset and adolescent-onset – when compared to those with late-onset schizophrenia, further supporting the neurodevelopmental hypothesis [11].

On the other hand, the cerebellum has long been acknowledged to play a central role in motor learning, an area of increasing attention in psychiatric research. This part of the brain, despite constituting only 10% of the brain's total volume, houses two-thirds of all neurons in our brain, illustrating its indispensable role. Consequently, the understanding of its functions has undergone a significant expansion throughout recent years. The cerebellum is believed to exert influence over various aspects of motor control, including regulation of voluntary limb movements, oculomotor control, prediction of sensory outcomes and sensorimotor synchronization [12]. While the knowledge of the roles of the cerebellum continue to evolve, extending beyond motor control to encompass cognitive functions and other higher-order actions, its participation in motor control has been increasingly elucidated too. For instance, we now know that the cerebellum is one of the first structures to undergo differentiation, yet paradoxically, it is also one of the last to fully attain maturity, rendering it particularly susceptible to disruptions during neural development [13]. That being stated, the motor abilities mediated by the cerebellum have been shown to reach maturity rather soon in neurodevelopment, thus these motor abnormalities could indicate a prompt cerebellar structure abnormality [14].

On the other hand, the conceptualization of the cerebellum in the pathogenesis of schizophrenia has been long theorized. Starting with Andreasen, who proposed a possible coordination impairment between the reception and information processing in psychosis, as a sort of cognitive dysmetria [15]. He hypothesized that there was a cerebrocerebellar circuit dysfunction leading to this alteration, and that the alteration of one component, in this case the cerebellum, may entail a universal dysfunction. Thus, the dysmetria of thought hypothesis suggests that the cerebellum acts as a universal modulator for behaviour, helping maintain a baseline level of functioning and that it depends on circuits taking place within the cerebrocerebellar system. When the cerebellar component in one of these neural circuits – emotional, cognitive or sensorimotor processing – is damaged, it universally impairs the specific domain involved [16].

Furthermore, the cerebellum remains extensively connected with nonmotor brain regions over our whole lives, indicated by its involvement in a wide range of cognitive processes, which seem to be notably relevant in psychosis pathology as well. One recent study highlighted

structural disparities in the cerebellum among psychotic patients who exhibit premorbid cognitive impairment, compared to those with a preserved cognitive function prior to onset [17]. They found these deficits were more prominently in motor lobules, possibly establishing a relation between the two, and its common cerebellum origin. Some studies have as well revealed that anatomical deficits in the cerebellum could predict general cognitive function and symptoms of psychosis in youths [18]. Additionally, case reports have been published which point to the fact that among individuals with cerebellar dysfunction there is a higher prevalence of psychotic disorders [19,20].

NSS also conventionally refer to non-localized abnormalities which have classically made it difficult to attribute them to a specific bran region. The brain network responsible for these abnormalities is still under investigation. The first study to be conducted with the aim of elucidating the underlying mechanisms of these signs took place in 1985 and compared the ventricle size measured by computed tomography and NSS, which was not conclusive. Later many studies using classical MRI and other more advanced techniques have reported structural abnormalities findings, mainly involving the cerebral cortex and its connections [21,22]. However, as previously stated, the crucial role of the cerebellum in motor coordination has been for long well-supported. Thus, the subsequent hypothesis is that its dysfunction may be primarily involved in the pathogenesis of these signs. Although a few studies have indeed found significant associations, the vast majority did not solely target cerebellar volume, but rather have a more general brain approach. A meta-analysis study summarizing all relevant findings pointed to a dysfunction on the cerebellum-thalamic-prefrontal network [23]. Some studies which have the cerebellum as the studied target reported that global soft sign severity was associated with volume reductions in the cerebellum in first episode psychosis patients [24] and one study specifically found a reduced volume in cerebellar posterior lobules [24].

Concerning medication, antipsychotic treatment is the central cornerstone in schizophrenia and other related psychoses, and its role in the presence of NSS has been long hypothesized. They carry out their therapeutic action via the blockade of Dopamine D2 receptors. This mechanism of action entails some motor side effects which can manifest either as extrapyramidal signs – such as dystonia, parkinsonism, akathisia and tardive dyskinesia –, or also as induced secondary negative symptoms – such as akinesia or bradykinesia. A study that compared individuals with Ultra-high risk for psychosis who were either being administered pharmacological treatment or not, show no significant differences in the prevalence and severity of NSS, which was further seen when compared both of this clinical groups with healthy subjects, supporting the notion that antipsychotic treatment do not

influence the appearance of NSS [25]. Other studies have also demonstrated that NSS persist unaltered in response to treatment with antipsychotics [26], even after patient stabilization. On the contrary, some studies have reported a light improvement in the NSS but never reaching levels typically seen in healthy subjects [27]. These findings indicate that these signs are more of an intrinsic disease feature rather than a side effect of neuroleptic therapy, and that they might be both trait and state related.

All of the above-mentioned works support an abnormal neurodevelopment as a key pathological pathway in psychosis. However, few studies were found that specifically correlated cerebellar structure with cerebellar function, and in the literature in general there is a lack of evaluation of the link between the three: treatment, cerebellum structure, and motor function.

In view of the previous discussion, with three main focuses, cerebellum involvement in motor function, psychosis and motor impairment and the possible effects of medications, this project aims to examine cerebellar structure in psychosis and explore the impaired motor functions possibly related to it. The primary objective is to elucidate the extent and specificity of cerebellar abnormalities in relation to motor impairment, while considering possible confounding factors like antipsychotic treatment side effects. Given prior research, the working hypothesis proposes that the cerebellar structure will exhibit greater alterations in individuals with more pronounced motor deficits, with no relation to treatment dosage, and that cerebellar structural alterations might serve as a biomarker for the risk of psychosis development.

3. METHODS AND MATERIALS

The procedures in this study were authorized by the clinical research ethics committee (CEIC) associated with the health areas of Valladolid.

a. Study Participants

This was a cross-sectional case series comparative study. A total of 19 participants were selected for the study. Before inclusion, all participants provided written informed consent. They were told that, if any previously undiagnosed clinical conditions were discovered during research, they would be appropriately noticed accordingly with their permission. The subjects were also informed that their involvement in the study was voluntary and that they could withdraw consent at any time. The clinical cohort was drawn from the Psychiatric Unit of the University Clinical Hospital of Valladolid and comprised patients who had received a confirmed diagnosis of psychosis, schizophrenia, bipolar disorder or schizoaffective disorder, as

ascertained through the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders 5th edition, considering clinical records and current mental state.

Individuals were excluded if they met any of the following criteria: an intelligence quotient below 70; a history of substance dependence, excluding caffeine and nicotine; and a history of head trauma resulting in loss of consciousness. Two individuals could not be considered in the statistical analysis due to missing cerebellar MRI analysis. The final clinical cohort were aged between 20-60 years, with an average of 39.4, and it was composed of 4 females and 15 males, with 2 males being further excluded from some of the statistical analysis.

b. Neurological soft signs assessment

Neurological soft signs were evaluated in all patients using the Neurological Evaluation Scale, developed by Buchanan and Heinrichs [28] in the Spanish version. The battery comprises 26 components, each rated on a scale ranging from 0 – not present – to 2 – severe –, 1 meaning mild impairment, except for the snout and suck reflexes, which are rated either 0 or 2. The items were further classified into three distinct functional areas attending at if the assessed sensory integration, motor coordination, and sequencing of complex motor tasks. Furthermore, this scale also included other aspects like short-term memory, abnormalities in eye movements, and frontal release signs, which have been frequently observed on these patients and are classified under another subgroup. Total scores were summed up and used to estimate the severity of impairment for the 26 items together. The subgroups and items pertaining to each one of them are shown in Table 1.

Sensory integration	Motor Coordination	Sequencing of complex motor tasks	Others	
Audio-visual integration	Tandem Walk	Fist-ring	Adventitious overflow test	Synkinesias
Sterognosis	Rapid alternating movements	Fist-edge-palm	Romberg test	Convergence
Graphesthesia	Finger-thumb opposition	Ozeretski	Tremor	Gaze impersistence
Extinction	Finger nose test	Rhythm tapping test	Memory	Glabellar Reflex
Right-Left Confusion			Rhythm tapping test	Grasp Reflex
			Mirror Movements	Suck Reflex

TABLE 1. NSS subgroups regarding the different functional areas affected.

c. Image acquisition and analysis

All patients were scanned for High-resolution 3-dimensional T1-weighted MRI using a Philips Achieva 3T MRI system (Philips Healthcare, Best, The Netherlands) equipped with a 32-channel head coil. For the acquisition of anatomical T1-weighted images, the following parameters were employed: Turbo Field Echo (TFE) sequence, with a repetition time (TR) of 8.1 ms, echo time (TE) of 3.7 ms, flip angle of 8°, a matrix size of 256 × 256, spatial resolution of 1 × 1 × 1 mm^3, and coverage of 160 slices spanning the entire brain. Resting-state functional MRI (rs-fMRI) data were acquired with a TR of 3000 ms, TE of 30 ms, flip angle of 80°, a matrix size of 80 × 80, spatial resolution of 3 × 3 × 4 mm^3, coverage of 35 axial slices spanning the whole brain, and consisting of 197 volumes. During rs-fMRI acquisition, participants were instructed to keep their eyes closed without falling asleep. All scans were conducted within the same session, commencing with the T1-weighted scan, followed by the diffusion-weighted scan and concluding with the rs-fMRI scan – the last two not utilized in this study. The total acquisition duration per subject was approximately 28 minutes, with a breakdown of six minutes for the T1-weighted scan, 12 minutes for the diffusion-weighted scan, and 10 minutes for the rs-fMRI scan.

Image data processing took place on Valladolid's University, led by the Telecommunications Engineering school, in collaboration with the SUCEDE group. Cerebellum volume was assessed using Free Surfer software, developed by the Laboratory for Computational Neuroimaging, on images T1-weighted. Structural scans were segmented into right and left cerebellum white matter, and right and left cerebellum cortex to calculate volume in mm3. Subsequently we added each hemisphere grey and white matter volume for unified comparison.

d. Antipsychotic dosage

Patient history was examined to obtain data regarding antipsychotic treatment regimens. Drugs and doses were noted. A standardized approach was employed to normalize treatment dosages across different antipsychotic agents, converting them into Chlorpromazine equivalents. The formula is shown in Figure 1. This way we were able to compare doses and measure their potential effects on the other variables. This methodology takes into consideration the potency of the different drugs and compares it to the efficacy of Chlorpromazine, based on their affinity for dopamine D2 receptors [29]. This data was collected on the date the Neurological Evaluation Scale was conducted for each participant, ensuring alignment between medication dosage and clinical assessment.

$$([Clozapine])x1 + ([Risperidone])x100 + ([Quetiapine])x0.8 + ([Olanzapine])x2 + ([Paliperidone])x50 + ([Aripiprazole])x25 + ([Haloperidol])x50 + ([Amisulpride])x0.25 + ([Ziprasidone])x2.5$$

FIGURE 1. Chlorpromazine equivalence equation for establishing equivalence.

e. Statistical Analysis

Statistical Analyses were performed using the Software IBM Statistical Package for the Social Sciences (SPSS), software version 23.0. For correlational analyses, Spearman's correlation analysis was used to identify correlations between NSS separated subgroups including total score for NSS and cerebellar tissue volume for each hemisphere and white or grey matter separately. No Kolmogorov-Smirnov test was performed due to the small sample size, so we assume the non-normal distribution hypothesis. Finally, we also determined the correlations between these cerebellar volume measurements and treatment dosage using a formula to calculate the Chlorpromazine equivalence for each patient. All tests were two-tailed with a confidence interval at 95%, and *p* was considered statistically significant if it was <0,05.

Scatter plots were generated using SPSS software to illustrate the correlations between NSS subgroups and total gray matter cerebellum volume. Additionally, Spearman's correlation tests were performed to assess the relationship between Antipsychotic dosage – expressed as Chlorpromazine equivalents – and NSS scores.

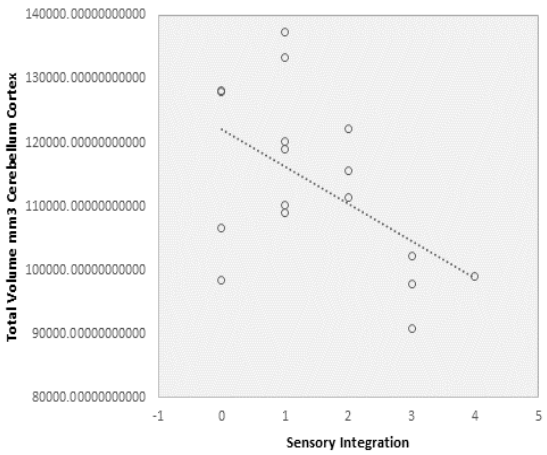
4. RESULTS

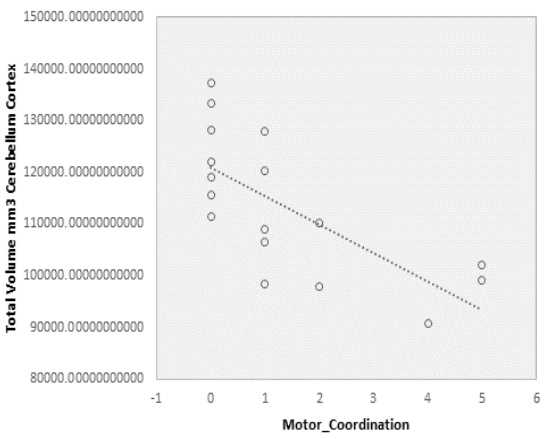
a. Correlation between NSS and Cerebellum volume

Statistically significant negative correlations were demonstrated in 10 of the 30 comparisons run. Overall, we found significant negative relationships between the majority of NSS subgroups and NSS total scores with Cerebellum volume, specifically concerning the cortical area, showing lower volumes in those patients with higher motor impairments. In particular, the bilateral associations between motor coordination and cerebellar gray matter would survive Bonferroni correction. With the exception of the "others" subgroup, who show no positive correlation with either the right or left hemisphere, the remaining NSS subgroups at least show one negative correlation. Notwithstanding, these non-statistically significant results, were all close to significance. This correlation was not observed when compare NSS subgroups and volume of white matter. Results of the analysis are summarized in Table 2 and representation of the correlations is depicted in Figure 2.

			LCWM	LCGM	RCGM	RCWM	vol_GM	vol_WM
Spearman's Rho	nss_si	Correlation Coefficient	-,198	-,426	-,504*	-,174	-,450	-,174
		Sig. (2-tailed)	,447	,088	,039	,505	,070	,505
		N	17	17	17	17	17	17
	nss_mc	Correlation Coefficient	,098	-,744**	-,783**	,137	-,759**	,121
		Sig. (2-tailed)	,708	,001	,000	,601	,000	,643
		N	17	17	17	17	17	17
	nss_st	Correlation Coefficient	-,088	-,529*	-,534*	-,045	-,508*	-,072
		Sig. (2-tailed)	,737	,029	,027	,865	,037	,784
		N	17	17	17	17	17	17
	nss_ot	Correlation Coefficient	-,014	-,412	-,434	-,010	-,419	-,044
		Sig. (2-tailed)	,958	,101	,082	,970	,094	,867
		N	17	17	17	17	17	17
	nss_total	Correlation Coefficient	-,099	-,522*	-,555*	-,058	-,525*	-,090
		Sig. (2-tailed)	,704	,032	,021	,826	,030	,732
		N	17	17	17	17	17	17

TABLE 2. Correlation between neurological soft signs (nss) and their subgroups, Sensory Integration (si), Motor Coordination (mc), Sequencing of Complex Motor Tasks (st) and others (ot), with volumes of the cerebellum, left cerebellum white matter (LCWM), left cerebellum cortex (LCGM), right cerebellum white matter (RCWM), right cerebellum cortex (RCGM), total cerebellum cortex volume (vol_GM) and total cerebellum white matter volume (vol_WM). The sig. (two-tailed) was considered significant when values were lower than 0.05. The table shows significant correlations with the value 0,05 (*) between LCGM and nss_sa, sns_total; RCGM and nss_is, nss_sa, nss_total; vol_GM and nss_sa, sns_total. Showing significant correlation with the value 0,01(**) between LCGM and sns_cm; RCGM and sns_cm; vol_GM and sns_cm.





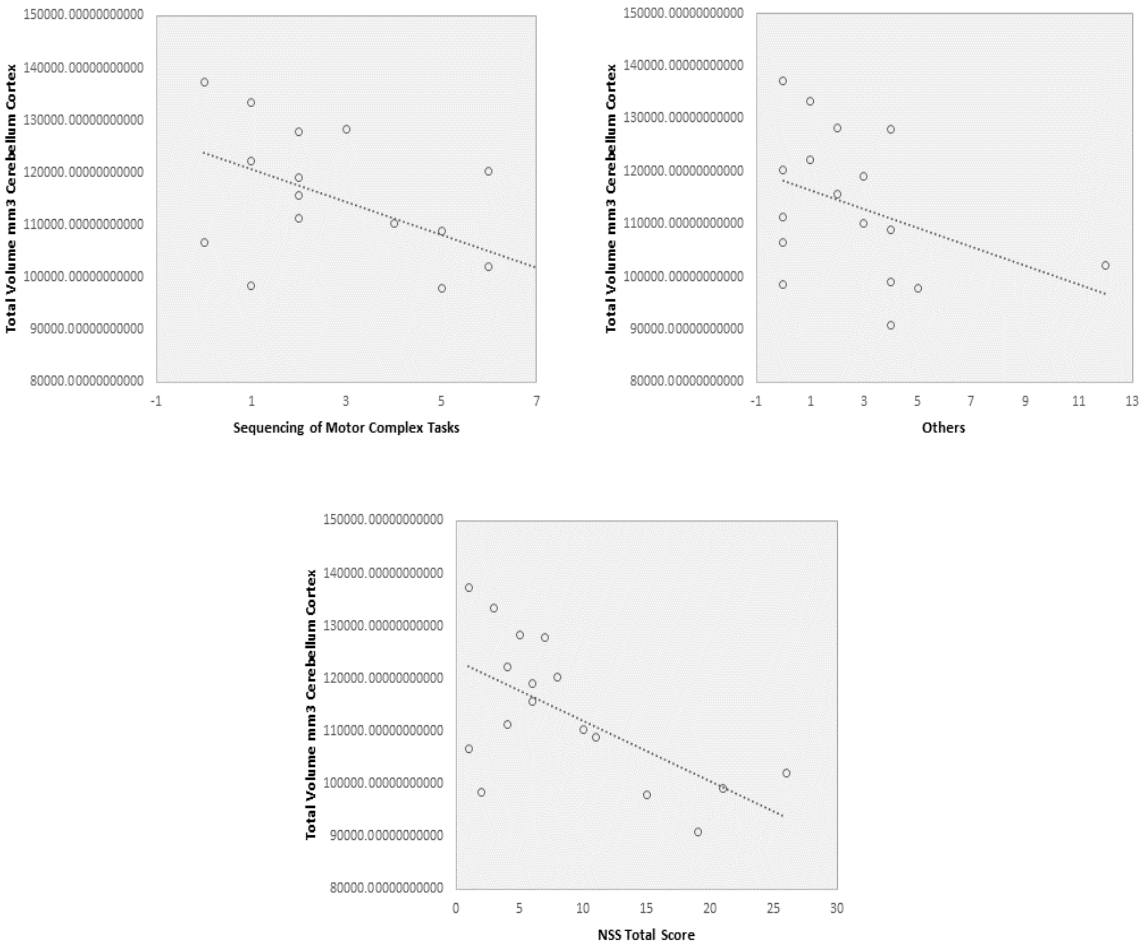


FIGURE 2. Scatter plots showing the association between variables, showing negative correlation between the subgroups of soft neurological signs in the x-axis and total cerebellum cortex volume (TCCV) in the y-axis. Sensory integration (is) and TCCV, (r = − 0,450); Motor coordination (cm) and TCCV, (r = − 0,759)**; Sequencing of complex motor acts (sa) and TCCV, (r = − 0,508)*; and others (ot) and TCCV, (r = − 0.419). NSS total score and TCCV (r = − 0,525) *. Correlation being significant with the value 0,05 (*) and 0,01(**).

b. Correlations between Antipsychotic treatment and Cerebellum Volume

No significant relationships were established between the distinct cerebellar volumes, neither gray nor white matter for either hemisphere, or the medication dosage received by each patient when compared. Results for the correlation are shown in Table 3.

		LCWM	LCGM	RCGM	RCWM	vol_GM	vol_WM
Chlorpromazine Equivalence	Correlation Coefficient	-,349	,146	,189	-,332	,166	-,355
	Sig. (2-tailed)	,169	,575	,467	,193	,524	,161
	N	17	17	17	17	17	17

TABLE 3. Correlation between antipsychotic dosage normalize as Chlorpromazine equivalents and cerebellum volume, subdivided into Left Cerebellum White Matter (LCWM), Left Cerebellum Gray Matter (LCGM), Right Cerebellum Gray Matter (RCGM), Right Cerebellum White Matter (RCWM), total volume of cerebellum Gray Matter (vol_GM), and total volume of cerebellum White Matter (vol_WM).

c. Correlations between Antipsychotic treatment and NSS

No significant associations between the different NSS functional areas and the medication dosage received by each patient arose. Correlation coefficients for this comparison are displayed in Table 4.

		nss_si	nss_mc	nss_st	nss_ot	nss_total
Chlorpromazine Equivalence	Correlation Coefficient	,029	-,172	-,103	,143	-,074
	Sig. (2-tailed)	,119	-,720	-,427	,598	-,305
	N	19	19	19	19	19

TABLE 4. Correlation between antipsychotic dosage normalized as Chlorpromazine equivalents and NSS functional regions scores: Sensory integration (nss_si), motor coordination (nss_mc), Sequencing of complex motor tasks (nss_st), others (nss_ot); and NSS total score (nss_total).

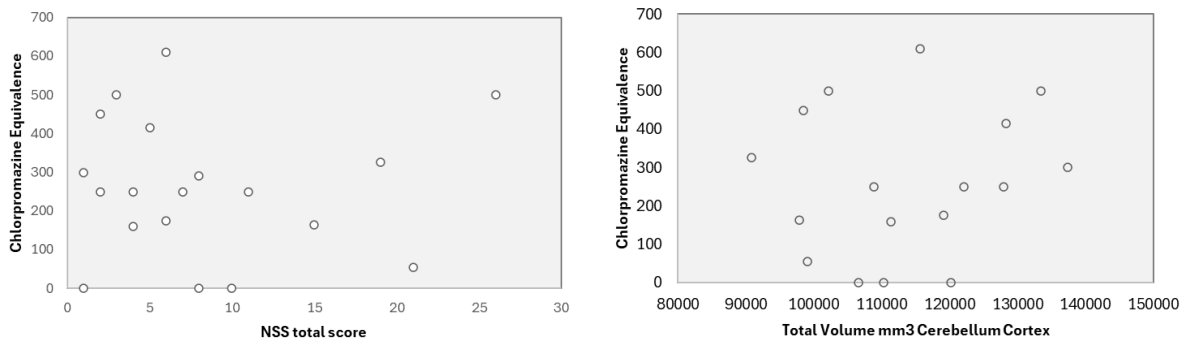


FIGURE 3. Scatter plots showing no significant relation between Chlorpromazine Equivalence with either NSS total score ($r = -0.355$, $p > 0.05$) or with total volume of cerebellum cortex ($r = -0.074$, $p > 0.05$).

5. DISCUSSION

The present investigation yielded one major finding: patients with psychosis exhibiting higher NSS scores displayed higher decreased volumes of both the right and left cerebellar cortical volume. The current study demonstrates a reduction in cerebellar volume among higher motor-impaired patients. This significant finding was also shown independent of antipsychotic

therapy which was excluded to be a potential confounding factor. This aligns with the previous assertions suggesting that NSS are present prior to diagnosis and manifestation of symptoms, being part of the underlying pathology rather than a result of the antipsychotic therapy.

Based on the observed distribution of statistically significant link between NSS with diminished volume, notably within the cerebellar cortex, it is plausible to hypothesize that cortical alterations within this brain region may represent a noteworthy pathophysiological pathway implicated in the onset of NSS. These findings could consequently suggest that such alterations may contribute to neurodevelopmental perturbations culminating in the manifestation of psychosis. Therefore, elucidating the mechanistic underpinnings of cerebellar cortical changes could shed light on the aetiology and progression of neuropsychiatric disorders, such insights may potentially inform therapeutic strategies aimed at addressing psychosis and related conditions.

Supporting these results, a study on Childhood-Onset Schizophrenia subjects found significant reduced cerebellar volumes, compared to controls, in line with the findings observed in adult-onset schizophrenia, supporting the notion of an early maldevelopment [30]. More recently some studies have shown that higher NSS scores in individuals with high-risk for psychosis prior to antipsychotic treatment are linked to decreased grey matter volume in several brain areas, including the cerebellum [31], supporting the independent nature of these changes of neuroleptics and the biological basis for psychosis. Consistent with this, another study identified a correlation, particularly between the overall severity of soft signs and reduced cerebellar gray matter density in patients naïve to neuroleptic medication with chronic schizophrenia. [32]. One study was found that did exclusively focused on the relationship between NSS and cerebellum and which included a control group, and reported, as expected, that higher scores in the former negatively correlated with volume of the posterior lobes of the cerebellum in psychotic patients, as opposed to control subjects who did not exhibit these associations [33].

Nonetheless, it is relevant to note, that although cerebellar structural abnormalities in psychosis have been addressed through numerous MRI and CT studies, the results remain somewhat inconclusive and frequently barely significant. Some studies did not find any significant correlation or found relation with white matter alterations. This lack of replication in structural correlates might be attributed to several factors, which include the low number of studies that focused on specific brain areas, and the considerable heterogeneity among patients. In line with this latter perspective, the National Institute of Mental Health recognized that new evidence indicated that in general psychiatric disorder categories were more like

heterogenous syndromes rather than specific diseases, and the current available diagnostic criteria could be detrimental to research, hindering the likeliness of identifying cerebral substrates due to irreplicability of samples [34]. So, studies which take into account this heterogeneity should be considered in the future. However, the active inclusion of patients with different diagnoses within the psychotic spectrum does supports something, and that is the idea that both affective as well as non-affective psychosis may share common neurobiological mechanisms.

There is abundant evidence that points to the fact that the cerebellum may play a key role in other neural circuits implicated in nonmotor functions, particularly higher-order functions, and thus, its involvement in the disorder may reach aspects beyond motor impairment. Emerging evidence suggests that the cerebellum partakes in cognitive development. Furthermore, several symptoms of psychosis have been conceptualized as deviations in the predictive mechanisms, another function in which the cerebellum is thought to play a crucial role. A systematic review of the evidence regarding this matter, extrapolate established mechanisms for predictive sensorimotor control to cognitive processes and extend their application to the development of psychosis. In this same study, they also discussed the finding that among individuals with cerebellar dysfunction – due to degeneration or infarcts –, there is a higher prevalence of psychotic disorders [35]. A recent study on the cerebellar structure in psychosis demonstrated a possible link between lower premorbid cognitive functioning and more prominent cerebellar structure abnormalities. The results showed differences in cerebellar structure between cognitively impaired psychotic patients in comparison with cognitively intact patients, and healthy subjects [17]. Some studies have as well revealed that anatomical deficits in the cerebellum could predict general cognitive function and symptoms of psychosis in youths [18]. This as well gives more support to an abnormal cerebellar development as a key pathological pathway in psychosis.

Also there is considerable heterogeneity when it comes to illness-stage, most studies, as the present one, did not focus on patients in their first-episode and, thus, results could be influence by chronicity [36] and neuroleptic treatments [37] since both may alter brain morphology. However, consistent with prior research, neuroleptic treatment was shown to unlikely exert an influence on either the occurrence and severity of NSS or the structural changes in cerebellar volumes. Previous investigations on the impact of neuroleptic treatment on brain structure revealed an increase in basal ganglia volume alongside reductions in various cortical regions, predominantly associated with typical antipsychotics, but they do not mention the cerebellum [37]. In line with these findings, extrapyramidal motor symptoms, but not NSS, have been

ascribed to an up-regulation of D2 dopamine receptors in the basal ganglia, a phenomenon observed during antipsychotic treatment. While extrapyramidal symptoms have exhibited a notable augment over the clinical course of psychotic disorders, NSS have been reported to even diminish with remission of acute symptoms, particularly more pronounced in those with remitting symptoms, although never reaching levels akin to healthy controls [27]. Following this paradigm, prior to initiating antipsychotic treatment, individuals with ultra-high risk of psychosis have been demonstrated to exhibit significantly reduced cerebellar volumes, implying a potential link between cerebellar atrophy and the behavioural manifestations - such as cognition and poor motor control - independent of psychotropic medication [38]. Additionally, reduced cerebellar volumes have been observed in unaffected first-degree relatives of individuals with psychotic disorders, emphasizing cerebellar alterations as a hereditary trait manifestation in these diagnoses [39].

Hence, rather than viewing NSS solely as a state or trait marker, it should be actively incorporated into patient management to enhance their quality of life. Moreover, some researchers have even proposed them as candidates for being an endophenotype specific to psychosis and thus might be used as identifiers of vulnerability. Endophenotypes in psychiatry refer to measurable traits that are believed to be closely linked to the underlying genetic susceptibility. They reflect the intermediate processes between the genetic predisposition and the clinical manifestations of psychosis. Thus, the co-appearance of NSS and cerebellum abnormalities – both present prior to the onset of psychotic symptoms –, and the association of the latter with certain factors such as more cognitive impairment and poorer premorbid state, manifestations common to psychosis, gives support to this theory.

Future studies employing alternative methods, such as diffusion-weighted imaging or molecular imaging, could provide additional insights into changes occurring in other brain regions, such as white matter ones. To better understand the connections between the examined factors and the appearance of NSS, upcoming research encompassing larger cohorts should combine various neuroimaging modalities.

6. LIMITATIONS

This work has several limitations. First, the clinical heterogeneity and small sample size should be considered. The sample size was small and only extracted from the population of Valladolid's University Clinical Hospital, which could restrict the generalization of findings. However, despite these limitations, the current sample allows to conclude that NSS are a common trait of psychosis across various disorders, rather than being exclusive to

schizophrenia. Furthermore, in general, neuroimaging abnormalities had a small effect size, thus, the significance obtained particularly with the cerebellar cortex should be taken into consideration.

Secondly, our analysis did not include factors such as age, which could contribute to alterations at the cerebellum cortical level [40]. Age as well as intelligence and education could have confounding effects on the NSS score. To add to that, there could also be significant intersubject variability in the NSS assessment due to illness-state, cognitive impairment, and interviewer bias. And despite evidence that NSS are relatively independent of antipsychotic therapy [26], their connection with extrapyramidal motor manifestations is still not well understood. There may be considerable overlap between the items among scales that assess neurological signs and those that evaluate extrapyramidal symptoms, leading to inconsistent results across studies.

Third, the absence of longitudinal data limited our ability to conduct a more detailed analysis of the progression of cerebellar abnormalities and its implications in individuals with psychosis. Consequently, this present study was unable to demonstrate the potential effects of the illness stage. While prior studies have hypothesized a degenerative character of the cerebellum in schizophrenia, besides the early neurodevelopmental lesions [41].

Finally, we also study the cerebellum as a whole, not accounting for the lobules particularly involved in control movement, hampering the possibility of finding more nuanced alterations. While previous studies have encountered more prominent alterations in specific regions, for instance in the posterior lobules of the cerebellum [24] .

Future research should aim to differentiate the effects of NSS from those demographic variables that may act as confounding factors and examine the stability of NSS throughout the progression of the illness to clarify its role in schizophrenia.

7. CONCLUSIONS

These results deepen our comprehension of the intrinsic characteristics of psychosis linked to NSS and may shed light on the pathophysiology preceding the onset of the disease. The findings lend support to the hypothesis that the cerebellum is involved in schizophrenia and suggest that the related changes within it are connected to NSS. They also support the notion that NSS are not exclusive to schizophrenia, and that there are common etiological processes involved in psychotic disorders. In summary our study contributes to a deeper understanding of the neurobiological underpinnings of psychosis, highlighting the role of NSS and cortical

volume, particularly within the cerebellum. These insights pave the way for future research endeavours aimed at elucidating the complex mechanisms underlying psychotic disorders and informing the development of targeted therapeutic interventions aimed at improving outcomes for affected individuals.

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RELACIÓN ENTRE ESTRUCTURA CEREBELAR Y FUNCIÓN MOTORA EN PSICOSIS

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INTRODUCCIÓN

Los trastornos psicóticos parecen vinculados a anomalías en el neurodesarrollo**.** La **disfunción motora** parece ser una característica intrínseca de la psicosis, estando presente en individuos antes del diagnóstico y sin exposición a antipsicóticos. Estudios del **cerebelo** también han demostrado **anormalidades estructurales** previos al inicio de la enfermedad y en pacientes diagnosticados. Dado el papel del cerebelo en la coordinación motora estos cambios podían estar relacionados.

OBJETIVO

Determinar la especificidad y extensión y las **anormalidades cerebelares** en relación con los **déficits motores** en pacientes con trastornos del espectro psicótico, teniendo en cuenta posibles factores confusores como la **medicación antipsicótica.**

MATERIALES Y MÉTODOS

DISEÑO

- Estudio Descriptivo, Transversal, Serie de casos

VARIABLES

- **Disfunción motora** → Signos neurológicos menores (SNM) → Escala de Evaluación Neurológica de Buchanan y Heinrichs
- **Estructura cerebelar** → Volúmenes cerebelares → Imágenes T1 RM con Software Free Surfer

Factor de confusión

- Dosis de medicación antipsicótica → Recogidos en el momento de la evaluación neurológica y transformados a Equivalentes de Clorpromazina (EC)

ANÁLISIS ESTADÍSTICO

Rho de Spearman → Correlación
- SNM y volumen cerebelar
- SNM y EC
- Volumen cerebelar cortical y EC

No siguen distribución normal → no prueba de Kolmogórov-Smirnov por pequeño tamaño muestral

PARTICIPANTES

Edad **39.4 ± 4.3** años

N=19

Diagnósticos DSM-5 →
- Esquizofrenia
- Trastorno bipolar
- Trastorno esquizoafectivo

RESULTADOS

		SNM	IS	CM	SA	OT	Total
Vol SG	*r*		-,450	-,759**	-,508*	-,419	-,525*
	p		,070	,000	,037	,094	,030
Vol SB	*r*		-,174	,121	-,072	-,044	-,090
	p		,505	,643	,784	,867	,732

Figura 1. Correlación entre SNM y volúmenes cerebelares. **Correlación significativa** entre volumen de sustancia gris *(Vol SG)* y coordinación motora *(CM),* Secuencia de actos motores complejos *(SA)* y puntuación total *(Total).* La asociación con integración Sensorial *(IS)* y otros *(OT)* no es significativa, pero está cerca de la significación (p<0.05). No hay asociación entre ningún SNM y el volumen cerebelar de sustancia blanca *(Vol SB).*
Coeficiente de correlación (r), significación bilateral (p).

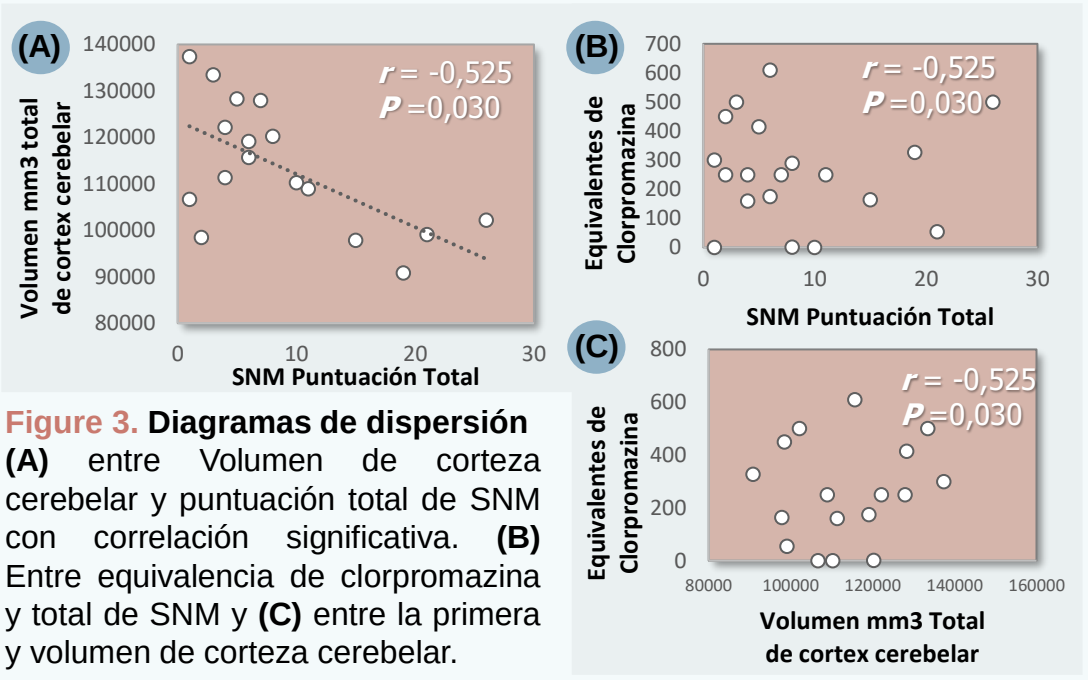

Figure 3. Diagramas de dispersión (A) entre Volumen de corteza cerebelar y puntuación total de SNM con correlación significativa. **(B)** Entre equivalencia de clorpromazina y total de SNM y **(C)** entre la primera y volumen de corteza cerebelar.

(A)	SNM	IS	CM	SA	OT	Total
Equivalentes de Clorpromazina	*r*	,029	-,172	-,103	,143	-,074
	p	,119	-,720	-,427	,598	-,305

(B) Volumen cerebelar		VSBI	VSGI	VSBD	VSGD	Vol_SG
Equivalentes de Clorpromazina	*r*	-,349	,146	-,332	,189	,166
	p	,169	,575	,193	,467	,524

Figure 2. **No asociaciones** entre **(A)** los equivalentes de clorpromazina y los subgrupos de SNM, **(B)** ni entre los equivalentes de clorpromazina los volúmenes cerebelares.
(A) Ver figura 1 para abreviaturas. (B) Volumen de sustancia blanca cerebelar izquierda (VSBI), volumen sustancia gris izquierda (VSGI), volumen de sustancia blanca cerebelar derecha (VSBD), volumen sustancia gris derecha (VSGD), volumen de sustancia gris total (Vol SG).

CONCLUSIÓN

Los **SNM** y la estructura de la **corteza cerebelar** están **relacionados**. La alteración motora y estructural cerebelar en los pacientes con psicosis es **independiente del tratamiento antipsicótico**. Además, los SNM aparecen en **todos** los pacientes con patologías del **espectro psicótico**, no siendo específicos de la esquizofrenia. Estudios previos sobre la implicación del cerebelo en psicosis parecen relacionarlo con otras manifestaciones de la enfermedad, por sus funciones **cognitivas** y otras funciones **superiores**. Por lo que los SNM pueden servir como un **endofenotipo**, reflejando el proceso intermedio entre la predisposición genética y la clínica de las psicosis, sirviendo como un marcador de riesgo. El cerebelo puede, por tanto, tener un papel fundamental en la fisiopatología de las psicosis.

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