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Featured Article

The Sant Pau Initiative on Neurodegeneration (SPIN) cohort: A data set for biomarker discovery and validation in neurodegenerative disorders

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Abstract

Introduction: The SPIN (Sant Pau Initiative on Neurodegeneration) cohort is a multimodal biomarker platform designed for neurodegenerative disease research following an integrative approach.

Methods: Participants of the SPIN cohort provide informed consent to donate blood and cerebrospinal fluid samples, receive detailed neurological and neuropsychological evaluations, and undergo a structural 3T brain MRI scan. A subset also undergoes other functional or imaging studies (video-polysomnogram, ^{18}F-fluorodeoxyglucose PET, amyloid PET, Tau PET). Participants are followed annually for a minimum of 4 years, with repeated cerebrospinal fluid collection and imaging studies performed every other year, and brain donation is encouraged.

Results: The integration of clinical, neuropsychological, genetic, biochemical, imaging, and neuropathological information and the harmonization of protocols under the same umbrella allows the discovery and validation of key biomarkers across several neurodegenerative diseases.

Discussion: We describe our particular 10-year experience and how different research projects were unified under an umbrella biomarker program, which might be of help to other research teams pursuing similar approaches.

The authors have no competing interests to declare that are relevant for this article.

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1. Background

Biomarkers have revolutionized our conceptualization of neurodegenerative diseases. In recent years, advances in the field of biomarkers have been instrumental in understanding the neurobiology underlying these disorders. Currently, biomarkers are essential to define the long preclinical stages, to achieve early diagnosis, to improve the selection of participants in clinical trials and to monitor the effect of drugs targeted to specific pathological pathways [1,2]. In the Sant Pau Memory Unit, as in many other teams specialized in neurodegenerative diseases, we have progressively adapted our clinical routine and research programs to incorporate the different biomarkers that are developed in the field. In this article, we describe our particular experience with this process and how the different research projects were unified under an umbrella biomarker program, which might be of help to other research teams pursuing similar approaches.

The Sant Pau Memory Unit is part of the Neurology Department at the Hospital de la Santa Creu i Sant Pau, a tertiary center that offers medical care to an area in Barcelona of approximately 400,000 inhabitants. In addition, the Unit is a referral center for complex or atypical cases around the Catalonia region. The Sant Pau Memory Unit attends patients with cognitive or behavioral symptoms referred either by their primary care physician or by other neurologists to receive specialized diagnosis and treatment and/or to facilitate their participation in research protocols.

Patients receive a standard initial medical visit by one of our faculty or fellow neurologists. Our initial visit consists of an extensive medical history revision, physical examination, and the administration of brief tests and questionnaires to assess cognition and functional impact in daily living activities. In most cases, in particular when cognitive impairment is not evident, a formal 1-hour cognitive evaluation by a neuropsychologist is scheduled, and sometimes, especially in patients with a suspected frontotemporal lobar degeneration–related syndrome or an atypical Alzheimer's disease (AD) syndrome, a specialized 2-hour additional visit helps to refine their clinical diagnosis. Neuroimaging and blood tests are also usually scheduled if they have not been previously ordered by their referral physician. In 2009, the clinical protocol was refined and cerebrospinal fluid (CSF) biomarkers were integrated to improve the early detection of prodromal AD. This approach facilitates the implementation of disease-modifying drugs that are currently under investigation in phase 2 or phase 3 clinical trials. After the completion of these tests, a follow-up visit is scheduled where results are discussed, diagnosis is disclosed, and an appropriate treatment is prescribed, if necessary. Patients and/or caregivers, usually receive an appointment with a nurse to enhance the understanding of treatment posology and eventually to clarify other medical, legal, or social aspects related to the disease.

As shown in Fig. 1, once the standard care has been ensured, most patients are invited to participate in research, either by enrolling in clinical trials involving new investigational drugs or in any of our observational research studies. Clinical trials are managed by a specific research team composed of neurologists, neuropsychologists, a research nurse, and a data manager. This team reviews inclusion/exclusion criteria and organizes follow-up appointments and drug administration according to each specific trial protocol. Participants of our observational studies, on the other hand, may receive ancillary biomarker and/or imaging tests and a specialized additional visit where supplementary questionnaires and cognitive/behavioral scales are administered. Our observational research studies include different neurodegenerative conditions and were recently reorganized under a global umbrella study named SPIN (Sant Pau Initiative on Neurodegeneration).

2. Methods

2.1. The SPIN cohort: General protocol

The SPIN cohort study was launched in 2011 as an umbrella program with the aim of grouping individual clinical observational studies performed in the Sant Pau Memory Unit. The SPIN cohort currently includes cognitively normal participants, patients with subjective cognitive decline, mild cognitive impairment, mild AD dementia, frontotemporal lobar degeneration–related syndromes (FTLD-S), dementia with Lewy bodies (DLB) and Down syndrome (which is treated in a separate section; see DABNI project). Inclusion and exclusion criteria for the SPIN cohort are detailed in Table 1. Patients with FTLD-S are systematically referred to the Motor Neuron Disease Clinic at the Neuromuscular Diseases Unit and evaluated by neurologists experienced in diagnosis and management of motor neuron diseases. A standardized visit is performed focusing on the detection of signs and symptoms suggestive of upper and lower motor neuron involvement. In these patients, an electrophysiological evaluation, including electromyographic concentric needle examination, motor and sensory nerve conduction studies are performed by qualified physicians according to established standards.

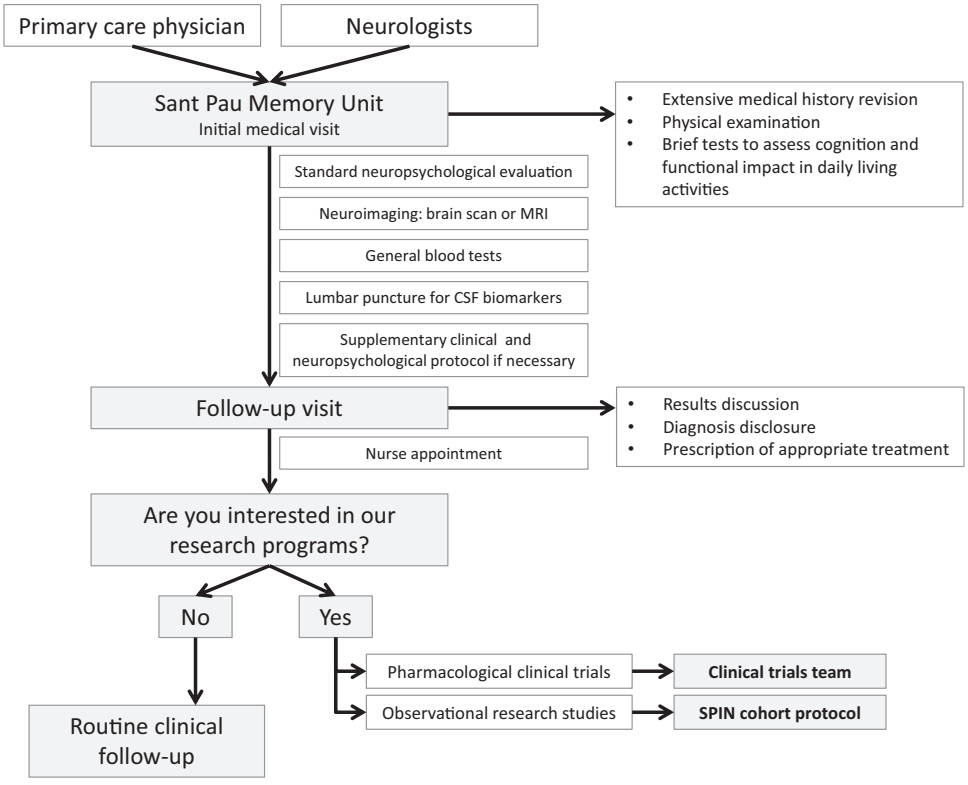

Fig. 1. Flow-chart of clinical practice and research protocols in the Sant Pau Memory Unit.

As the primary objective of the SPIN cohort is biomarker discovery and validation, consent for blood and CSF collection is required for all participants. Detailed neurological and neuropsychological evaluation and a structural 3T brain MRI are also necessary for inclusion. As shown in Fig. 2, a subset of participants receive a video-polysomnogram and/or imaging tests that involve radiotracers, such as ^{18}F-fluorodeoxyglucose (^{18}FDG), amyloid or Tau PET. Participants are followed on an annual basis for a minimum of 4 years, and we offer the possibility to repeat imaging and/or CSF studies every two years.

2.2. Cognitively normal volunteers

Asymptomatic volunteers are an extremely relevant group in the SPIN cohort. Volunteers are usually spouses or children of patients that are informed about our studies at the outpatient clinics of the Sant Pau Memory Unit. Volunteers can also learn about our projects through talks, our website (https://santpaumemoryunit.com) or social media (@SantPauMemory).

All volunteers receive an initial consultation with a neurologist in which the SPIN protocol is explained in detail, inclusion/exclusion criteria are reviewed and informed consent is signed. As in other observational studies, the SPIN cohort has a blinded design and biomarker results are not disclosed to volunteers unless clinically relevant or in case the participant becomes eligible for pharmacological prevention clinical trials.

On the first day, a neurologist and a neuropsychologist perform a full medical history review, physical examination, and a standard neuropsychological evaluation (Table 2) followed by a lumbar puncture and blood extraction. Neuroimaging studies might be scheduled on different days.

To minimize the impact of the study on volunteers' routine, all participants can choose how they prefer to be informed of the results, either by post, email, or by scheduling an extra on-site appointment. Those participants whose neuropsychological evaluation, biochemical analysis, or neuroimaging studies show clinically relevant abnormal results are scheduled for an on-site consultation to discuss these results. Cognitively normal participants are contacted annually for a minimum of 4 years, and they are invited to repeat neuropsychological, imaging, and CSF studies every two years.

2.3. Ethical aspects

At the moment of inclusion in our observational studies, the details of the protocol are explained, and verbal and signed informed consent is obtained from all participants. We specifically ask all participants for their consent to the acquisition, analysis, and storage of biological samples. They are also informed about the possibility of sharing anonymized information and/or biological samples with other researchers, which is requested in an independent consent form. The original protocol and the

Table 1
Inclusion and exclusion criteria for the SPIN cohort

Inclusion criteria
For all participants
18 years or older
Signed informed consent
Cognitively normal controls
No memory complaints
MMSE [27–30]
CDR global score = 0
FCSRT total immediate score (EAS62) ≥ 7
Absence of significant impairment in other domains or in daily living activities.
Subjective cognitive decline
Memory complaints (severe enough to have resulted in a request for medical referral)
MMSE [27–30]
CDR global score = 0
FCSRT total immediate score (EAS62) ≥ 7
Absence of significant impairment in other domains or in daily living activities.
Prodromal AD
MMSE [24–30]
CDR global score = 0.5
Absence of a clinical diagnosis of dementia
CSF biomarkers supporting AD pathophysiology
Typical AD dementia
CDR global score ≥ 0.5
FCSRT total immediate score (EAS62) ≤ 6
Clinical criteria of "probable AD dementia with evidence of the AD pathophysiological process" [59]
Dementia with Lewy bodies
Lewy body dementia: probable Lewy body dementia [60] or Lewy body mild cognitive impairment: Mild cognitive impairment [61] AND one or more of: - Visual hallucinations - Parkinsonism - REM sleep behavior disorder - Cognitive fluctuations [62]
Frontotemporal lobar degeneration–related syndromes (FTLD-S)
Possible, probable, or definitive behavioral variant of frontotemporal dementia [63]
Semantic variant of primary progressive aphasia [64]
Nonfluent/agrammatic variant of primary progressive aphasia [64]
Corticobasal syndrome [65]
Progressive supranuclear palsy syndromes [66,67]
Any of the clinical diagnoses along the amyotrophic lateral sclerosis–frontotemporal dementia (ALS-FTD) continuum [68,69]
Down syndrome
Presence of trisomy at chromosome 21
Exclusion criteria
• Inability to complete neuropsychological tests and questionnaires (illiteracy, blindness, hearing impairment) • Contraindication for MRI (claustrophobia, pacemaker, aneurism clips, cardiac mechanical valve) • Contraindication for lumbar puncture (anticoagulation, coagulation disease): Must not be taking anticoagulant treatment such as acenocoumarol, heparin, warfarin, dabigatran, rivaroxaban, apixaban • Current treatment with drugs that can impair cognition • Medical history of: ○ Neurological disease (stroke, brain lesions, epilepsy) ○ Psychiatric disease (psychosis or major depression) ○ Drug abuse in the last year ○ Medical history of cancer is an exclusion criterion when: ■ It affects the central nervous system ■ It has not been in complete remission for 5 years or longer ■ Patient has received potentially neurotoxic chemotherapy ■ Patient has received cranial radiotherapy

Abbreviations: AD, Alzheimer's disease; CSF, cerebrospinal fluid; EAS62, education-adjusted score at the age of 62 years [70]; MMSE, Mini–Mental State Examination; CDR, Clinical Dementia Rating; FCSRT, Free and Cued Selective Reminding Test; SPIN, Sant Pau Initiative on Neurodegeneration.

SPIN cohort protocol	BASELINE	YEAR 1	YEAR 2	YEAR 3	YEAR 4
Revision of inclusion and exclusion criteria	Required	-	-	-	-
Protocol revision and general consent signature	Required	-	-	-	-
Medical history revision	Required	Update	Update	Update	Update
Clinical examination	Required	-	Required	-	Required
Neuropsychological evaluation	Required	Required	Required	-	Required
General blood test	Required	Required	Required	-	Required
Blood extraction for plasma/serum/genetics	Required	-	Optional	-	Optional
Lumbar puncture for CSF biomarkers	Required	-	Optional	-	Optional
Brain MRI	Required	-	Optional	-	Optional
^{18}F-Fluorodeoxyglucose PET	Optional	-	Optional	-	Optional
Amyloid PET	Optional	-	Optional	-	Optional
Tau PET	Optional	-	Optional	-	Optional
Sleep evaluation and real world evidence data	Optional	-	Optional	-	Optional

Fig. 2. General protocol in the SPIN cohort. Abbreviations: SPIN, Sant Pau Initiative on Neurodegeneration.

subsequent amendments were approved by our local ethics committee. The SPIN cohort is based on blinded enrollment and only clinically relevant biomarker results are disclosed.

2.4. Neuropsychological evaluation

All participants in the SPIN cohort receive a standard one-hour neuropsychological evaluation to assess episodic verbal memory, visual memory, attention, executive functions, visuospatial, visuoperceptive and visuoconstructive functioning and language. Neuropsychiatric symptoms, functional impact, and the level of global cognitive impairment are also assessed. Table 2 lists all tests included in our standard neuropsychological evaluation [3].

Our standard protocol includes two verbal memory tests that are sequentially administered to maximize the detection of prodromal AD: the Free and Cued Selective Reminding Test (FCSRT) and, after a nonverbal interference task, the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) word list when the former is within normal range. We have found that the combination of these two tests can improve the early detection of AD and define prognostic profiles in mild cognitive impairment [3].

Participants with a diagnosis of DLB or FTLD-S receive an additional neuropsychological evaluation to further investigate cognitive functions that are particularly impaired in these disorders, such as visuoperceptive functions and fluctuations in DLB or language, behavior, and executive functions in FTLD-S (Table 2).

2.5. Cerebrospinal fluid

Lumbar puncture for CSF sampling is required for all participants of the SPIN cohort. CSF is collected and processed in polypropylene tubes following international recommendations [4,5]. The first 2 ml of CSF are transferred to the general laboratory for cell count, and analysis of glucose and protein levels. Another volume of 15-20 ml is transferred to our laboratory where samples are processed and aliquoted within the first two hours after the lumbar puncture. Aliquots are stored at −80°C until analysis. Full protocol for CSF processing is detailed in Fig. 3A.

Core AD biomarkers (Aβ1-42, t-Tau, and p-Tau) are routinely measured in all participants. Our clinical cutoffs for core AD biomarkers were initially obtained from a group of 70 patients clinically diagnosed with dementia of the Alzheimer type (whose clinical diagnoses were made blind to biomarker results) and 45 age-matched cognitively normal controls. Our internal cutoffs were calculated using ELISA [6], transferred to fully automated platforms and validated in a sample of patients that underwent amyloid PET [7]. Our laboratory participates in the Alzheimer's Association quality control program for CSF biomarkers [8,9].

2.6. Blood and DNA extraction

All participants in the SPIN cohort have blood drawn at the time of lumbar puncture. Fasting is not required before the extraction, but the time from last meal to blood extraction is recorded. All samples are transferred to our laboratory where they are centrifuged and aliquoted within 2 hours after

Table 2
Clinical and neuropsychological evaluation protocols

Standard neuropsychological evaluation
Screening tests
Mini–Mental State Examination [71,72]
Memory Alteration Test [73]
Episodic verbal memory*
Free and Cued Selective Reminding Test (FCSRT) [70,74]
Consortium to Establish a Registry for Alzheimer's Disease (CERAD) word list [75]
Visual memory
Complex Rey Figure Recall [70,76,77]
Geometric Figures recall from the Consortium to Establish a Registry for Alzheimer's Disease or CERAD battery [75]
Attention/executive functions
Phonemic verbal fluency test [78,79]
Trail-Making test form A and B [80]
WAIS Direct and Reverse Digit span [80]
Clock Drawing Task on command [81]
Language
Boston naming test [82,83]
Consortium to Establish a Registry for Alzheimer's Disease or CERAD battery (orders comprehension) [75,84]
Semantic verbal fluency [78,79]
Visuospatial/visuopercetpive/visuoconstructional functioning
Geometric figures copy subtest of CERAD
Number location subtest from the Visual Object Space and Perception (VOSP) battery [85]
Poppelreuter overlapping figures test [86]
Neuropsychiatric symptoms
Neuropsychiatric inventory [87]
Geriatric depression scale [88]
Functional assessment
Interview for deterioration in daily living in dementia [89]
Global cognitive impairment
Global deterioration scale [90]
Clinical dementia rating [91]
FTLD-specific Clinical Dementia Rating [92]
Additional neuropsychological evaluation in LBD patients
Visual Object Space and Perception (VOSP) battery [85]
Line Orientation Test
Facial Recognition Test
Pareidolia Test
Clinician Assessment of Fluctuation
Additional clinical and neuropsychological evaluation in FTLD-S patients
Standardized neurological examination (CATFI protocol) including UPDRS-III [93]
Separate clinical interview with at least 1 reliable informant for a precise determination of the chronology of both cognitive and behavioral signs and symptoms [94]
Frontotemporal Dementia Rating Scale [95,96]
In ALS-FTD patients: Edinburgh Cognitive and Behaviour ALS Screen (ECAS) [97,98]
Extensive language evaluation (audio recorded)
Progressive Aphasia Language Scale [99,100]
Spontaneous speech and description of Boston cookie theft picture test [84]
Standardized examination of Apraxia of Speech including alternating movement rate and sequential motion rate tasks [101]
Repetition of sentences and pseudowords [84]
Syntactic processing [84]
Pyramid palm and trees test [102,103]
Extended phonemic verbal fluency test [78,79]
Narrative writing of the Boston cookie theft picture [84] and free extensive narrative writing without time constraints (1 full A4 page)
Spanish adaptation of the New Adult Reading Test named "Test de acentuación de palabras" [104]
Attention/executive functions
Design fluency of the D-KEFS battery [105]
Stroop test [106]
Frontal Assessment Battery [107]
Behavior and mood
Frontal Behavioral Inventory [108]
Informant version of the Lille Apathy Rating Scale [109]
Cambridge Behavioral Inventory Revised [110]
Brief questionnaire of Socioemotional Dysfunction

Abbreviations: ALS-FTD, amyotrophic lateral sclerosis–frontotemporal dementia; FTLD-S, frontotemporal lobar degeneration–related syndromes; CATFI, Catalan Initiative for Frontotemporal Dementia; UPDRS-III, Unified Parkinson's Disease Rating Scale, Part III (motor examination).

*Tests that assess episodic verbal memory are administered sequentially separated by a nonverbal interference task.

extraction and stored at −80°C until they need to be analyzed. Full protocol for blood processing is detailed in Fig. 3B.

DNA is extracted from whole blood samples using the DNeasy® *Blood & Tissue* kit (Qiagen). *APOE* genotype is routinely determined for all participants in the SPIN cohort by direct DNA sequencing of exon 4 and visual analysis of the resulting electropherogram is performed to identify the two coding polymorphisms that encode the three possible apoE isoforms. Other genetic studies in the SPIN cohort involve mendelian genes related to neurodegenerative dementias (i.e., *PSEN1*, *PSEN2*, *APP*, *C9orf72*, *MAPT*, *VCP*, etc.), as well as other genes and genomic regions that have been involved in their genetic architecture, such as *TREM2* [10], *CHCHD10* [11], *TUBA4A* [12], or the 17q21.31 region around *MAPT* [13]. High-throughput genotyping and next-generation sequencing technologies are also used in specific studies [14,15].

2.7. Structural, diffusion, and functional MRI

All participants in the SPIN cohort are required to undergo 3T-MRI for structural, diffusion, and resting-state functional MRI. Acquisitions parameters are detailed in Table 3.

Our neuroimaging core takes advantage of surface-based methodologies to process MRI images. Structural MRI is processed using FreeSurfer software package (v6.0; http://surfer.nmr.mgh.harvard.edu) to obtain individuals' cortical reconstruction and cortical thickness maps by using previously described methods [16]. Estimated surfaces are then inspected to detect possible errors in the automatic segmentation procedure, and manual edits are performed to guarantee an accurate cortical segmentation.

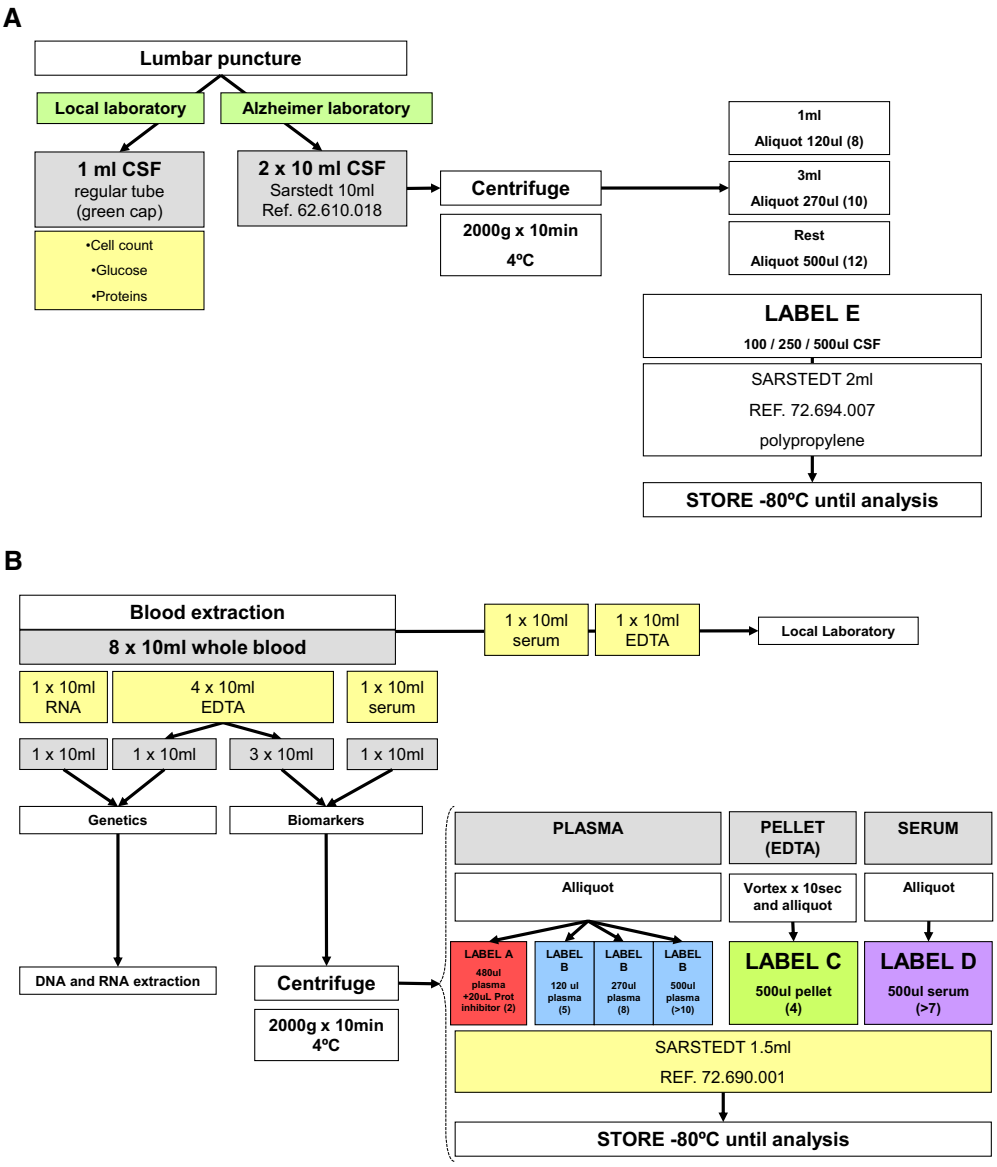

Fig. 3. Biofluid processing: protocols for cerebrospinal fluid (A) and blood (B).

Diffusion images are processed with a surface-based in-house developed algorithm [17,18] based on FSL (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki) and FreeSurfer tools. Our pipeline computes cortical diffusivity metrics that allow the evaluation of microstructural changes in the cortex, mitigating some of the pitfalls caused by usual voxel-based methodologies. Resting-state functional MRI studies are processed with an in-house algorithm specifically developed for these sequences [19]. This pipeline admits procedures commonly used in functional imaging studies such as seed analysis and independent component analysis.

2.8. *Nuclear medicine imaging: ^{18}FDG PET, amyloid PET, Tau PET*

Studies with ^{18}FDG PET are acquired in a subset of participants to measure brain metabolism. These studies are visually rated by an expert in nuclear medicine, and images are also processed and quantified by our neuroimaging team. For the whole-brain voxelwise analysis, ^{18}FDG PET images are intensity-scaled by the reference pons-vermis region, spatially normalized using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/) to the Montreal Neurological Institute PET template and spatially smoothed with a Gaussian kernel of full width at half maximum 8 mm. All resulting images are visually inspected to check for possible registration errors. The quantitative analysis of ^{18}FDG uptake in a specific region of interest is performed following the methodology proposed by Landau et al. [20–22].

Over the past few years, new tracers have been developed to visualize *in vivo* specific neuropathological aggregates. In the SPIN cohort, amyloid PET studies with ^{18}F-florbetapir have been acquired for a subset of participants, and more recently, we have incorporated ^{18}F-flutemetamol and tau

Table 3
MRI acquisition parameters for structural, diffusion, and functional MRI

MRI acquisition parameter	Structural T1 MRI	Diffusion-weighted imaging MRI	Resting-state functional MRI
Protocol	MPRAGE	Echo-planar Imaging	Echo-planar Imaging
Repetition Time (ms)	8.1	13,677	200
Echo Time (ms)	3.7	61	31
Slices	160	80	21
Slice thickness (mm)	1	2	4 (1 of gap)
Voxel Size (mm)	0.94×0.94×0.94	2×2×2	2.4×3.3×4
Specific Parameters	-	Single b = 0 image. 32 gradient directions with b = 1000. One inverted phase encoding b = 0	190 volumes. Eyes open.

Abbreviation: MPRAGE, magnetization-prepared rapid acquisition with gradient echo.

tracers. Images are visually rated by experts in nuclear medicine, and specifically developed semiautomated quantification protocols are applied [7]. Briefly, amyloid PET images are spatially normalized to the subject's T1-MRI and then to the Montreal Neurological Institute 152 template using the individual's anatomical MRI coregistration. Global amyloid PET standardized uptake value ratio scores are estimated averaging frontal, cingulate, parietal, and temporal cortices and using the whole cerebellum as the reference region [23]. In addition to the commonly used analyses in PET using voxel-based and region-based approaches, we have added surface-based methodologies that substantially improve the reliability of PET effects and reduce the intersubject variance.

2.9. Sleep evaluation and real-world evidence data

Cognitively normal volunteers in the SPIN cohort and participants with Down syndrome are invited to undergo a full sleep evaluation with subjective and objective measures of the nocturnal sleep and the circadian sleep-wake pattern. This evaluation includes an interview with a sleep specialist, a full nocturnal video-polysomnography, and actigraphy. Participants are requested to track their sleep-wake pattern in sleep diaries and to answer sleep questionnaires designed to assess participants' self-reported sleep quality (Pittsburgh Sleep Quality Index), somnolence (Epworth Sleepiness Scale) and to identify participants at risk for sleep apnea syndrome (Berlin Questionnaire). Video-polysomnography studies are performed in individual, sound-attenuated, temperature-regulated sleep unit rooms under continuous supervision of qualified technical staff. All-night video-polysomnography records information from 19 electroencephalographic channels, two oculographic electrodes, four surface electromyographic channels, and six sensors to monitor respiratory function by assessing oximetry, oronasal airflow, thoracoabdominal movements, and snoring detection. The week before the polysomnography, participants wear an actigraph in the nondominant arm to monitor rest/activity cycles. These portable devices record data on levels of daily activity and light during 24 hours. They provide information about total sleep time and sleep efficiency that can be compared with subjective sleep diary reports and objective polysomnographic data.

2.10. Neuropathology

All participants in the SPIN cohort are encouraged to consent for brain donation. In follow-up visits, we stress the importance of neuropathological studies to advance the research of neurodegenerative diseases and suggest all participants contact the Barcelona's Neurological Tissue Bank (http://www.clinicbiobanc.org) for formal registration.

Neuropathological validation is a critical issue in multimodal biomarker studies. Brain donation not only allows the confirmation of the diagnosis and the presence of comorbid pathologies but is also necessary to correlate pathological data with CSF or imaging biomarkers [24] and to characterize the underlying biological processes of these biomarkers [25]. Moreover, it is known that secondary pathologies can influence the biomarker signatures [26,27], and it is important to capture them for their correct interpretation.

In our group, we have implemented array tomography microscopy, which is based on obtaining ultrathin (70 nm) consecutive brain sections combined with immunofluorescence [28,29]. Array tomography requires special fixation conditions, which limits the availability of samples for this type of study. This technique has been previously applied to successfully evidence synaptic abnormalities in AD and, more recently, in DLB [30–33].

2.11. Data integration

One of the strengths of the Sant Pau Memory Unit is that we have integrated clinical, neuropsychological, biomarker, genetic, neuroimaging, and neuropathological information from subjects with different neurodegenerative disorders in one single database. Every participant receives a unique code to integrate all the information. As all data are associated to specific time points for each participant, information from different categories can easily be combined, and automated ready-to-analyze anonymized datasheets can be obtained.

2.12. The Down-Alzheimer Barcelona Neuroimaging Initiative: DABNI

The Alzheimer-Down Unit was founded in 2014 as an alliance between the Sant Pau Memory Unit and the Down Syndrome Catalan Foundation. The specific purpose of this Unit, the first of its kind in the world, is the assessment of adults with Down syndrome by medical professionals specialized in dementia for the detection of AD. This multidisciplinary Unit, formed by neurologists, neuropsychologists and social workers, has been recognized by the Catalan government as the reference hospital in Catalonia for the assessment of neurological disorders associated with Down syndrome.

Taking advantage of the SPIN cohort structure, the Alzheimer-Down Unit launched a parallel comprehensive biomarker study entitled "Down-Alzheimer Barcelona Neuroimaging Initiative" (DABNI). The aim of the DABNI project is to improve our understanding of the mechanisms that drive AD in Down syndrome (http://fcsd.org/).

3. Results

Our database includes neuropsychological data of more than 6000 participants, genetics data of more than 3200 participants, more than 2600 blood samples from 2100 participants, and more than 2000 CSF samples from 1700 participants. Neuroimaging information of over 1100 MRI studies, more than 800 FDG-PET and 200 amyloid PET are also incorporated and matched to clinical, neuropsychological, genetic, and biomarker information.

CSF samples from the SPIN cohort have contributed to several international multicenter CSF biomarker studies [34–38]. The SPIN cohort has contributed to the characterization of different CSF biomarkers such as β-site APP-cleaving enzyme activity [39,40], sAPP-β [6,39,41], neurofilament light chain [41], YKL-40 [6,39,41–43], progranulin [44], a panel of synaptic proteins [45], and mitochondrial DNA [46] in different neurodegenerative diseases. In addition, the collection of paired blood and CSF samples offers the possibility to investigate the correlation of biomarker levels between these two compartments [15,44]. In addition, our DNA repository has been involved in many international studies aimed at identifying the genetic basis of neurodegenerative disorders [47–50].

Imaging MRI studies acquired in the SPIN cohort have contributed to multicenter collaborative studies [17,42,51], and their combination with other biomarkers has yielded relevant results regarding multimodal relationships [41,42,44]. Our neuroimaging team has also developed and described novel methods for the detection of longitudinal changes in cortical structure [52] and cortical microstructural changes in diffusion-weighted sequences in AD and FTLD-S [17]. Nuclear medicine imaging studies have also contributed to several international multicenter imaging biomarker initiatives [53–57].

The incorporation of sleep evaluations in some of the SPIN cohort clinical groups has yielded clinically relevant results. For example, in participants with Down syndrome, questionnaires do not completely reflect sleep disturbances detected on polysomnography, and data acquired by actigraphy might be more sensitive to detect daytime sleep compared with self-reported scales [58].

Access to brain tissue in subjects with antemortem imaging or with biofluid biomarkers also offers the possibility to look into innovative clinical-pathological correlations. The addition of a sophisticated neuropathological quantitative technique such as array tomography microscopy to a multimodal biomarker program has opened the possibility of correlating biomarkers with detailed neuropathological traits. As an example, in the future, we could correlate amyloid load measured by amyloid PET with synaptic densities in different brain regions or a synaptic protein in CSF with synaptic densities postmortem.

4. Discussion

The organization of the Sant Pau Memory Unit is in many aspects similar to other units across the globe. However, there are some key aspects that are specific to our Unit and that may have been instrumental in achieving certain objectives.

First, the current size of our unit (around 35 members) allows daily interaction and collaboration under a manageable environment. Larger organizations tend to divide into smaller groups, hampering daily interaction and limiting the possibilities of collaboration. Also, the research cores, such as genetics, biofluid, imaging, or neuropathology, are developed inside the Unit, which facilitates the flow of projects and collaborations. Second, our projects are performed in a highly multidisciplinary environment that facilitates cross-fertilization and the generation of new ideas. Third, our members hold a collaborative spirit and share leadership. The experience and knowledge of consolidated researchers are complemented by fresh and innovative approaches of younger researchers. Finally, our hospital environment provides our research with a clinical patient-focused perspective, which helps in keeping a holistic view on neurodegenerative diseases.

The SPIN cohort is a multimodal biomarker platform designed to study neurodegenerative diseases under a holistic approach. The integration of clinical, neuropsychological, genetic, biochemical, imaging, and neuropathological information and the harmonization of protocols under the same umbrella has allowed the discovery and validation of key biomarkers for these diseases. The data generated are crucial to understanding the pathophysiology of neurodegenerative diseases and to improve their diagnostic and prognostic assessment.

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RESEARCH IN CONTEXT

1. Systematic review: Literature was reviewed through PubMed and meeting abstracts. In the past decade, different research teams have launched multimodal biomarker cohorts to improve diagnosis in neurodegenerative diseases. We provide extensive references for the specific protocols and methods used in the SPIN cohort.
2. Interpretation: The integration of clinical, neuropsychological, genetic, biochemical, imaging, and neuropathological information and the harmonization of protocols under the same umbrella allows the discovery and validation of key biomarkers across several neurodegenerative diseases. We describe our particular 10-year experience and how different research projects were unified under an umbrella biomarker program, which might be of help to other research teams pursuing similar approaches.
3. Future directions: Longitudinal integrative data in the SPIN cohort will be of help to further understand the pathophysiology of neurodegenerative diseases and to improve their diagnostic and prognostic assessment.

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