Functional Connectivity and BOLD Variability as Neural Biomarkers for Cancer-Related Cognitive Impairment

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***Abstract*—Cancer-related cognitive impairment (CRCI), often referred to as 'chemo brain', is a frequently reported but poorly understood side effect in breast cancer survivors, characterized by deficits in attention, memory, and executive function. This thesis aims to evaluate resting-state functional connectivity (FC) and BOLD signal variability (SD-BOLD) as potential neural CRCI biomarkers. Three open-access datasets were analysed, one of which includes raw resting-state fMRI data from 31 healthy female controls aged 50-63, as well as pre-processed group-level results from breast cancer survivors. A custom pre-processing pipeline was applied, as well as the extraction of the FC and SD-BOLD measures across the hippocampus and key cognitive networks (salience network, frontoparietal network, default mode network). Correlation analyses and group comparisons were performed against cognitive scores (e.g. California Verbal Learning Test (CVLT) for memory and the Rosenberg Self-Esteem Scale (SES). The results did not show any significant association between memory and hippocampal FC in healthy controls, nor were differences detected between the high and low memory groups for FC. In contrast, SD-BOLD in the anterior insula exhibited strong negative correlations with executive function ($r \approx -0.60$) and memory ($r \approx -0.40$), and significantly distinguished between high- and low-memory performers ($p = 0.044$). While this study is exploratory, it provides initial evidence that SD-BOLD is a promising CRCI biomarker, warranting further validation in cancer patients with multimodal, longitudinal studies.**

***Index Terms*—cancer-related cognitive impairment, resting-state fMRI, BOLD signal variability, functional connectivity, salience network, neural biomarkers**

I. Introduction

A. Clinical Background: What Is Cancer-related cognitive impairment?

Cancer-related cognitive impairment (CRCI), often referred to as *'chemo brain'*, is a frequently reported but poorly understood side effect experienced by many non-central nervous system (non-CNS) cancer survivors, particularly those treated with chemotherapy. It refers to a range of cognitive problems that can be experienced during and after treatment. It most commonly affects memory (such as forgetfulness), attention (such as difficulty focusing and being easily distracted), and executive function (such as problems with planning, multitasking and decision-making) [1]. These symptoms can vary in severity and duration between patients.

Unlike brain tumors, CRCI occurs in patients with non-CNS cancers (e.g. breast, prostate, colorectal), meaning cognitive side effects can arise even when the cancer is outside the brain [2]. It is most commonly reported in survivors of breast cancer, especially in those who have undergone chemotherapy.

Chemotherapies such as cisplatin, doxorubicin, methotrexate, and carboplatin can cause neurotoxicity, vascular dysfunction, and inflammation, which can all potentially alter brain activity and increase the variability of the fMRI signal (e.g. SD-BOLD) [3], [4]. Furthermore, hormonal therapies commonly used in breast cancer, such as tamoxifen, can cause disruptions in estrogen signaling in the brain, potentially impairing cognition and influencing BOLD signal dynamics [5].

CRCI is often subjectively reported by patients; however, objective neuropsychological assessments do not always confirm the deficits [2]. This discrepancy makes diagnosis more difficult, as there may be patients who feel impaired even though their results are within the norm. It is mainly due to this mismatch that CRCI is so difficult to define and study. According to systematic reviews, about 75% of patients experience cognitive problems during their cancer treatment, and about 35% of patients continue to have impairments long after therapy ends [6]. However, there is no agreement on how we should define and measure CRCI clinically [7]. Despite CRCI having a significant impact on the daily functioning and quality of life of many patients, it remains an understudied topic. The absence of diagnostic criteria, the inconsistent use of cognitive tests, and the limited application of neuroimaging have hindered progress in understanding the neural basis of CRCI [8], despite growing evidence that CRCI affects multiple cognitive domains and has a significant impact on survivors' quality of life [9], [10]. Identifying brain-based biomarkers would allow earlier detection and more personalized care strategies.

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B. Why Brain Imaging? The Case for functional MRI

In the field of medical diagnosis, neuroimaging is a crucial tool in understanding brain disorders and has become essential in CRCI research. It allows researchers to visualize brain changes associated with cancer and its treatments,for example by identifying neural biomarkers such as altered connectivity and reduced brain volume. [2].

Overall, it plays a key role in decoding the neural changes of CRCI and allows earlier detection, monitoring, and potential intervention.

One such neuroimaging technique is the non-invasive method functional magnetic resonance imaging (fMRI). Particularly useful in CRCI is the resting-state fMRI (rs-fMRI). This does not require task performance, making it ideal for patients who are cognitively impaired. It shows altered functional connectivity (FC) and reduced signal variability (SD-BOLD), both of which are strongly associated with CRCI. The strength of fMRI lies in the fact that it is sensitive enough to detect subtle, therapy-induced alterations in brain function that are not always visible on structural scans, making it a very useful method for uncovering the cognitive impact of cancer treatments.

C. Current Gaps in Research

Despite increasing interest in CRCI, there are critical gaps that limit research progress, such as inconsistent definitions and unclear diagnostic criteria. Due to patient privacy, the number of publicly available datasets is very limited, especially for students and beginning researchers.

Combining modalities such as EEG and fMRI is promising, however they are often infeasible due to financial, technical, or data availability limitations. Therefore, EEG has not been included in this thesis. Although we have seen increasing progress in identifying neural biomarkers; the discovery of reliable and universally accepted neural biomarkers continues to be a challenge [11]. The International Cognition and Cancer Task Force (CCTF) has highlighted the need for clear CRCI definitions, consistent cognitive tests, and more data sharing. These recommendations have yet to be fully implemented across studies.

D. Thesis Focus and Scope

Given these limitations in neuroimaging research and the clinical relevance of CRCI, this thesis focuses on evaluating rs-fMRI data to further investigate functional brain-changes associated with CRCI. It specifically targets breast cancer survivors, the population in which CRCI is most frequently reported and studied, to ensure consistency of comparisons and more reliable assessment of therapy-induced cognitive alterations. The thesis examines the two neural measures, seed-based functional connectivity (FC) and BOLD signal variability (SD-BOLD), both evaluated as potential biomarkers for CRCI. The research analyzes an open-access rs-fMRI dataset that includes cognitive performance scores and compares the findings to published group-level results from CRCI studies. This structured approach aligns new analyses with established CRCI studies to evaluate the relevance of FC and SD-BOLD as potential biomarkers.

To improve the scientific aspect of this thesis, it is guided by three predefined hypotheses, which have been derived from CRCI literature [2], [6], [10], [12], [13]. The hypothesis questions target the salience network, hippocampal connectivity, and BOLD variability. All hypotheses are explored through correlation analyses and structured group comparisons.

Identifying a biomarker is highly valuable, even when no therapy exists yet, as is the case for SD-BOLD and FC. Early detection allows identifying the individuals at risk, monitoring cognitive changes over time, and preparing for personalized care strategies such as cognitive training, lifestyle adjustments, or workplace modifications. Additionally, biomarkers are essential for future treatment trials, as they allow tracking of therapy effectiveness and selecting suitable candidates for interventions.

E. Justification for Using Healthy Controls

Although only the healthy female control group is analysed in this thesis, rather than the breast cancer survivors directly, this design allows us to, even in the absence of disease, test whether FC and SD-BOLD are reliable indicators of cognitive performance, which is a necessary first step in validating them as general biomarkers. The aim of this study is not to directly diagnose CRCI. Instead, we aim to assess whether neural features are sensitive to cognitive functioning in general. If meaningful variation in cognitive performance within a healthy population is captured by these features, it provides evidence that they may also be sensitive to the subtler, therapy-induced alterations that are seen within CRCI.

This indirect strategy is necessary because of data limitations, since open-access, high-quality CRCI datasets are scarce. In contrast, healthy control datasets are more widely available and offer a controlled environment without the confounds of cancer treatment. This allows for a clean assessment of how brain metrics relate to cognition.

By testing whether these measures relate to natural cognitive variation in healthy individuals, we can assess the general sensitivity of resting-state FC and SD-BOLD. In case no relation with cognition in healthy controls is shown by a neural measure, it may reflect CRCI-specific disruptions. However, if a metric captures meaningful variation even in healthy individuals, it strengthens its potential as a general and early biomarker of cognitive dysfunction. By using this approach, we not only complement published CRCI patient findings, but also provide a baseline for interpreting biomarker relevance.

F. Aim and Research Questions

The aim of this thesis is to identify changes that therapy causes in brain function and to investigate the potential of FC and SD-BOLD as CRCI biomarkers. By using computational methods applied to rs-fMRI, it evaluates FC and SD-BOLD in the context of cognitive performance. The work focuses on these three research questions:

1) What therapy-induced alterations in resting-state brain activity can be identified in cancer patients through computational analysis of functional connectivity and signal variability in fMRI data?
2) Can these computationally extracted features serve as neural biomarkers for cancer-related cognitive impairment (CRCI)?
3) How well do these neuroimaging-derived features correlate with cognitive performance, and can data-driven methods reveal meaningful patterns or predictive relationships?

To operationalize these research questions, three further hypotheses were tested, focusing on SN variability, hippocampal connectivity, and group-level FC and SD-BOLD differences.

G. Biomarkers of Cancer-Related Cognitive Impairment: Functional Connectivity and BOLD Signal Variability

Functional connectivity refers to the temporal correlation between the BOLD (blood-oxygen-level-dependent) signal time series of different brain regions, usually measured in rs-fMRI. In a healthy brain, the FC is usually higher, indicating stronger temporal synchrony and more potential for effective communication.

In CRCI, however, a higher FC is not necessarily a sign of a healthy brain. In fact, it can mean the opposite, as a high FC in CRCI may reflect compensation for damage, such as increased activity in memory-related brain regions as a response to the damage. Decreased FC, on the other hand, usually means that communication is disrupted, and it goes hand in hand with cognitive decline.

There are multiple studies that state that FC is altered in breast cancer survivors who have undergone chemotherapy. Specifically, this involves large-scale cognitive networks [12]. These changes are linked to objective as well as subjective cognitive impairment. This supports FC's potential as a CRCI biomarker. Studies reported that in cancer survivors who have undergone chemotherapy, reduced connectivity was found within this region, particularly in relation to verbal memory impairment [2].

Given the hippocampus's role in memory formation and recall, as well as its vulnerability to aging and treatment effects, the hippocampus was included in this thesis as a candidate region for evaluation of the biomarkers [13].

Outside of CRCI, FC has already been explored as a biomarker in non-cancer disorders such as Alzheimer's disease, depression and ADHD. These studies show that FC consistently shows disease-related changes and is a promising prospect in early detection and symptom mapping [14]. Nonetheless, its clinical use is still limited due to variability and the lack of standardization.

SD-BOLD refers to the standard deviation of the BOLD signal over time in a brain region, measured in fMRI. When a brain region is activated, the amount of oxygen in that region increases. Higher variability is usually associated with greater neural flexibility and better cognitive performance.

Recent studies on breast cancer survivors have reported reduced SD-BOLD in patients who have undergone chemotherapy and report cognitive complaints, especially in networks involved in the executive function and attention [3]. Additionally, BOLD variability is a sensitive neural processing biomarker, but shows the need for rigorous noise reduction to ensure true neural dynamics are reflected by SD-BOLD rather than noise [15]. Although SD-BOLD is not a widely explored measure in CRCI research, past studies have tested SD-BOLD as a functional biomarker in other disorders such as aging, schizophrenia, and ADHD. For example, SD-BOLD has been shown to be sensitive to preclinical Alzheimer's disease biomarkers and to correlate with neurodegeneration markers, reinforcing its potential as a biomarker in cognitive disorders [14]. Thus, while SD-BOLD has not yet been tested as a potential biomarker for CRCI, these studies suggest that it can be a promising candidate due to its sensitivity to therapy-related cognitive changes.

According to the FDA/NIH Biomarkers Definitions Working Group, "a biomarker is a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions." In the context of neuroimaging, an effective biomarker should meet the following criteria [2]: 1. Sensitivity, the biomarker's ability to detect small changes in brain function. 2. Specificity, the biomarker's ability to distinguish its target condition, in this case CRCI, from other causes of cognitive change, such as aging. 3. Reproducibility, the biomarker should yield consistent results across different studies, subjects, and settings. 4. Clinical relevance, the biomarker should reflect meaningful information about the patient's condition.

Although FC has been studied in CRCI and SD-BOLD has been mentioned in a few studies, neither measure has been evaluated as a CRCI-specific predictive or diagnostic biomarker [7]. Most CRCI studies that use neuroimaging focus on reporting differences between patients and control groups, such as connectivity, but they do not assess whether these differences have predictive or diagnostic value.

In this thesis, that gap will be addressed, by testing FC and SD-BOLD as potential biomarkers for CRCI, while using computational methods to evaluate their relationship with cancer survivors' cognitive performance.

H. Network Disruptions in Cancer-Related Cognitive Impairment and Beyond

In recent years, CRCI's understanding has shifted from isolated regional damage to a disorder of large-scale brain network dysfunction. "The human brain is organized into large-scale networks that dynamically interact to facilitate cognitive function, with core systems such as the default mode network, frontoparietal network, and salience network playing key roles in attention, memory, and executive control." [16]. As Menon's definition states, these networks are essential for higher-order cognitive functions. The Default Mode Network (DMN) is involved in memory and self-referential processing.

The Frontoparietal Network (FPN) supports attention, working memory, and executive function. The Salience Network (SN) facilitates cognitive control and switches between brain networks based on task demands. Disruptions in these networks may underlie cognitive problems reported by cancer survivors, even without visible brain damage.

There are CRCI studies in which both FC and SD-BOLD changes were observed in these core networks. In the FPN, FC and SD-BOLD are reduced, possibly reflecting damage to attention and executive function. In the DMN, it often shows either reduced or abnormally increased FC, which may indicate difficulty in processing internal thoughts or compensatory activity. In the SN, although less studied, changes were also reported, with potential impairments to the brain's ability to switch between task and resting-state networks. These findings show that CRCI involves a widespread pattern of network-level dysfunction [6], [10], [13], measurable by either FC or SD-BOLD, possibly underlying the diverse symptoms reported by survivors.

The spatial distribution of the key regions is illustrated in Fig. 1 (see Appendix), to help contextualize these network disruptions. As these networks are involved in key cognitive processes, their dysfunction provides potential as a target to identify impairment related to CRCI. Similar disruptions have been found in other disorders such as Alzheimer's disease, depression, and ADHD. This further highlights their relevance for brain-based cognitive dysfunction. Since CRCI affects the same networks, it strengthens the case for targeting them in biomarker evaluation. Identifying consistent dysfunction across these systems can support earlier CRCI detection and personalized interventions.

In Alzheimer's disease, FC in the DMN decreases with memory impairment and disease progression, supporting its biomarker potential. Similarly, SD-BOLD was studied in schizophrenia and ADHD. In schizophrenia, it was linked to symptom severity and cognitive dysfunction. In ADHD, reduced SD-BOLD was associated with impaired attention control and executive function. In these studies, group comparison and cognitive correlations are commonly used to assess relevance. This thesis mirrors these validated approaches by comparing cancer survivors with healthy controls and examining how FC and SD-BOLD relate to performance. By using established methodologies from other disorders, this thesis evaluates FC and SD-BOLD as candidate CRCI biomarkers, where formal validation is still lacking.

Despite growing interest in CRCI, validated neural biomarkers have not yet been established. FC and SD-BOLD seem promising, but most studies stop at group-level differences without testing predictive value. Disruptions in core brain networks have been observed, yet their use in biomarker development remains under-explored. Therefore, FC and SD-BOLD need to be evaluated head-to-head.

This thesis addresses that by building on findings from other disorders in which FC and SD-BOLD were evaluated. It aims to fill the CRCI gap by applying similar methods, such as group comparisons and cognitive correlations, contributing to the search for neural biomarkers.

Although FC and SD-BOLD changes have been reported, most studies investigate them in isolation. Regarding FC, there are inconsistencies (e.g. decreases as dysfunction vs. increases as compensation), and few studies assess how well cognition is predicted by these measures. This thesis addresses that by comparing FC and SD-BOLD directly in the same individuals and evaluating associations with cognition - an approach that is rarely used in CRCI.

II. Methods

A. Datasets

Our analysis uses three publicly available datasets, including fMRI data and cognitive performance scores. All datasets were selected based on their relevance to CRCI research, as well as the availability of female participants, due to the clinical profile of breast cancer survivors. Across all datasets, the ages of the participants were in the range of 50–63, providing a comparable age group for analysis. The following datasets were selected:

Dataset 1: **Brain Sciences dataset** – This study analysed preprocessed fMRI data from 27 female breast cancer survivors who underwent chemotherapy, as well as 28 healthy female controls [3]. No raw data was available, only the published group-level results (e.g., ROI-level FC and SD-BOLD values) were used for comparison in this thesis. Cognitive functioning was assessed using the Functional Assessment of Cancer Therapy – Cognitive Function (FACT-Cog), and the Montreal Cognitive Assessment (MoCA). The study analysed FC and SD-BOLD measures based on the preprocessed rs-fMRI scans. Imaging was performed on a 3T Siemens Verio scanner with TR = 2000 ms and 3.5 mm^3 voxel size.

Dataset 2: **Brain Imaging and Behavior dataset** – This dataset includes 33 female breast cancer survivors and 28 healthy controls [17]. Similarly to Dataset 1, no raw imaging data was available for this thesis, and only the reported group-level findings were used for comparison. All participants underwent validated neurocognitive testing procedures to assess memory, attention and executive function. Imaging was performed on a 3T GE Discovery MR750 scanner with TR = 2000 ms and 3 mm^3 voxel size.

Dataset 3 (Healthy controls): **PEARL-Neuro dataset** – This dataset contains 192 healthy individuals [18]. They are classified "healthy" based on the dataset's metadata, which included limited and demographic health-related information, however, no formal clinical health screening was performed as part of the dataset. Of these, 79 participants had neuroimaging data available. To match the clinical profile of breast cancer survivors, only female participants with available rs-fMRI were selected for this thesis, resulting in a final subset of 31 participants. This dataset contains raw rs-fMRI data, as well as extensive cognitive assessments such as the Beck Depression Inventory (BDI) which tests depression, California Verbal Learning Test (CVLT) which measures memory, and Rosenberg's Self-Esteem Scale (SES) which approximates executive function. The data, unlike the other two datasets,

has not been pre-processed, and all imaging analysis steps will be performed as part of this thesis. This dataset is used as a healthy control reference group, which can be compared to the breast cancer survivors from the other datasets. MRI data was acquired using a Siemens Prisma 3T scanner with TR = 2400 ms and 0.8 mm^3 voxel size.

To ensure all datasets are comparable, given their different style, this thesis aligned key methodological parameters across studies where possible. This includes using identical FC and SD-BOLD seed regions for feature extraction, mimicking statistical analysis approaches, normalizing cognitive scores to enable comparison across different datasets.

For the breast cancer survivor cohorts, we relied on published results (ROI connectivity values and SD-BOLD means) as raw data were not available. Only reported group-level findings were compared to minimize the risk of confounds in pre-processing pipelines or scanners.

B. Pre-processing

Given that each dataset was independently analysed, no cross-scanner correction or harmonization methods were required. Only the PEARL-Neuro dataset underwent quantitatively imaging analysis in this thesis, while the two datasets were used only for comparison at the reported group level. By analysing each dataset independently and without pooling raw imaging data, we minimized scanner-related confounds, while still allowing comparison to published findings on group-level.

The data in the Brain Sciences and Brain Imaging and Behavior dataset are pre-processed, as the original studies already applied standard pipelines. The reported pre-processing steps included slice timing correction, motion correction, temporal filtering with a band-pass filter of [0.01, 0.08] Hz in 'Brain Sciences' and [0.01, 0.15] Hz in 'Brain Imaging and Behavior', and spatial normalization to standard space. No additional pre-processing techniques, such as smoothing, were performed in this thesis, as the dataset was published with finalized imaging analysis. The PEARL-Neuro dataset on the other hand, contains only raw data in BIDS format, requiring full pre-processing.

As the dataset does not include T1w scans, standard pipelines such as fMRIPrep, which require structural reference images for spatial normalization were not applicable for this dataset. Instead, a lightweight custom pre-processing pipeline was implemented using FSL and Python-based tools, and the analyses were performed in native functional space (the participant's original brain coordinates, without spatial normalization), avoiding potential misalignment from low-quality normalization. This approach reflects standard rs-fMRI practices and aligns with the analytic strategies used in the articles corresponding to Dataset 1 and 2.

A 6mm FWHM Gaussian kernel was chosen for spatial smoothing, as it offers a balance between spatial resolution and signal-to-noise enhancement. Smaller kernels (e.g. 4mm) risk preserving too much noise, while larger kernels (e.g. 8mm) may oversmooth individual variability, which is critical for CRCI.

Due to the absence of physiological recordings such as heart rate or respiration, correction methods such as RETROICOR [19] could not be applied. Instead, strict motion correction and minimal de-noising were used to preserve true neural variability, which is essential for the estimation of SD-BOLD. Due to the risk of removing neural signal of interest, more aggressive denoising such as CompCor or ICA-AROMA was avoided.

C. Feature Extraction

The neural feature extraction in this thesis focuses on FC and SD-BOLD. These features were extracted due to their relevance to CRCI in previous studies, as well as their availability across the selected datasets. The feature extraction followed the same pre-processing constraints described earlier, including the use of native functional space for the PEARL-Neuro dataset. For all selected participants within this dataset, FC was computed as the Pearson correlation between the mean BOLD signal in the seed and all other voxels. SD-BOLD was calculated voxel wise as the standard deviation over time.

FC Feature Extraction – To examine resting-state connectivity, a seed-based FC approach (a method that measures connectivity from predefined brain regions) will be used. Resting-state FC has been widely applied in cognitive neuroscience and supports both predictive modeling of cognitive outcomes and group-level comparisons [20]. For each participant in the PEARL-Neuro dataset, connectivity maps will be computed by correlating the mean BOLD time series of a predefined seed region with that of all other brain voxels. In networks that are relevant to CRCI (DMN, FPN, SN), seeds are selected. Pearson correlation coefficients will be computed and transformed with Fisher's r-to-z transformation (a statistical transformation for correlation coefficients), allowing statistical comparison at group level. To follow standard rs-fMRI methods and ensure reproducibility, seed regions across the DMN, FPN, SN, and hippocampus were selected based on prior CRCI studies [21]. MNI coordinates and ROI definitions are detailed in Table I (see Appendix) for clarity.

SD-BOLD Feature Extraction – For each participant, SD-BOLD is calculated voxel-wise as the standard deviation of the preprocessed BOLD signal over time [15]. This measure is extracted using the same preprocessing pipeline as FC, allowing for direct comparison between the measures. As explained in the former sections, SD-BOLD offers complementary insight to cognitive function and neural flexibility, and will be explored across the same CRCI-relevant networks of interest (DMN, FPN, SN).

Voxel-wise SD-BOLD computation has been validated as a reliable and sensitive fMRI metric in prior literature [15], ensuring its methodological robustness within this thesis.

Seed-based FC was chosen for its targeted evaluation of brain regions relevant in CRCI and is widely used in neuroimaging research, allowing for comparability with prior CRCI studies.

D. Cognitive Data

The PEARL-Neuro dataset includes participants' cognitive performance scores that are relevant to CRCI research.

The California Verbal Learning Test (CVLT) scores are analyzed as the primary measure for memory. The Rosenberg Self-Esteem Scale (SES) score was used to approximate executive function as a surrogate marker. Although SES does not directly test executive function, self-esteem can reflect confidence in cognitive abilities, which is relevant for CRCI research. This is acknowledged as a limitation. These scores will not be recalculated. Instead, they will be used for correlational analyses with the FC and SD-BOLD measures, to observe their relationship with cognitive performance. The other two datasets report group-level cognitive performance results and will be used for group comparison by comparing the cognitive scores of cancer survivors against controls, where applicable.

E. Statistical Analysis

The analyses focus on the FC and SD-BOLD measures across the networks of interest. All analyses are implemented with Python and its built-in packages such as NumPy, Pandas, SciPy, and Nilearn. Where needed, False Discovery Rate (FDR) correction [22]will be applied to account for multiple comparisons. As the thesis focuses on exploratory analyses, and not predictive modelling, no machine learning models will be used.

Uncorrected thresholds were reported to show prior trends, while FDR-correction was used to confirm robustness against multiple comparisons. Solely the results that bypassed the FDR-correction were interpreted as statistically significant.

III. Experiments

To test the research hypotheses, we designed experiments to evaluate brain–cognition relationships using correlation and group comparison analyses.

The statistical analysis was guided by the following three hypotheses:

1) **H1**: Higher SD-BOLD in the salience network will correlate with lower cognitive scores.
2) **H2**: Hippocampal connectivity will positively correlate with CVLT scores.
3) **H3**: The low-CVLT group will show increased BOLD variability in the insula compared to the high-CVLT group.

Using these hypotheses, appropriate statistical tests were performed, including Pearson correlation for neural-cognitive associations and independent samples t-tests (Welch's t-test) for group comparisons. All results were evaluated at uncorrected and FDR-adjusted thresholds to assess robustness.

The experiments were designed to mirror the analyses performed in the two processed datasets. By adopting this structure, we ensured that our findings could be interpreted within an established framework and directly compared with published CRCI results.

Correlational analyses were chosen to test continuous relationships between cognition and brain measures, while group comparisons were used to examine whether neural metrics were able to distinguish between high and low memory performance—an approach that reflects standard biomarker evaluation practice.

IV. Results

A. Functional Connectivity and Cognition (H2)

Given the hippocampus's role in CRCI and its inclusion in H2, the finding that there are no FC-memory links in healthy individuals indicates that hippocampal disruptions only appear in cancer-affected brains. In our healthy control group, no significant correlations were discovered between hippocampal FC and memory performance, which was measured by CVLT1 (the immediate recall score from the first trial of the California Verbal Learning Test). The left hippocampus showed a weak positive association ($r \approx 0.24$, $p \approx 0.20$), unlike the right hippocampus, which showed no correlation ($r \approx 0.00$, $p \approx 0.98$), as displayed in Table II (see Appendix). In other regions, such as the medial prefrontal cortex (mPFC) and lateral parietal cortex, FC did not show significant correlations with the cognitive scores either. This suggests that resting state FC was not a strong predictor of memory in this healthy group.

The group comparisons between high and low CVLT-score performers did not show a significant difference in FC across any of the examined regions. Fig. 2 (see Appendix) illustrates that the hippocampus and SN regions showed weak or no correlation between FC and cognitive scores. The group comparisons also confirmed that these regions were largely comparable between high and low CVLT performers (most $p > 0.6$, full results in Table III, with a visual example in Fig. 3 (see Appendix for both)). These results further indicate that memory performance was not differentiated by FC in this healthy sample.

Altogether, these results do not support H2, as hippocampal FC did not show significant correlation with memory scores and did not differentiate between high and low CVLT performers in the healthy control group.

B. SD-BOLD and Cognition (H1)

SD-BOLD in the bilateral insula showed significant negative correlations with cognitive performance. Specifically, higher anterior insula variability was associated with lower memory scores on CVLT1 ($r \approx -0.40$, $p < 0.03$), and lower self-esteem (SES), with robust correlations for the left insula ($r \approx -0.60$) and right insula ($r \approx -0.59$), both of which were statistically significant after False Discovery Rate (FDR) corrections ($p < 0.0001$). These findings show that higher variability, possibly meaning neural instability, was associated with worse cognitive performance. The anterior cingulate cortex (ACC) showed a similar negative pattern with the CVLT1 scores ($r \approx -0.29$), however this association did not reach statistical significance ($p \approx 0.12$). The described correlation patterns are summarized in Table IV (see Appendix). Although group comparisons are primarily addressed in H3, Fig. 4 (see Appendix) is referenced here to display the observed insula variability differences between memory groups. These findings

support H1, meaning that higher resting state SD-BOLD in salience network regions, particularly the anterior insula, is associated with worse cognitive function in healthy controls.

C. Group Differences in SD-BOLD (H3)

To test the final hypothesis, participants were divided into high and low memory scores based on their CVLT1 performance. This comparison was done to discover potential differences in neural measures on group-level. The independent samples t-test showed that participants in the group with low CVLT scores had significantly higher SD-BOLD in the left anterior insula compared to the group with high CVLT scores (mean $\approx$ 7.91 vs 7.39, $p = 0.044$, 95% CI for the mean difference $[0.014, 1.024]$). This difference at group-level is illustrated in Fig. 4, which displays higher insula variability in the low-memory group. In contrast, no significant differences in FC were observed between the high and low CVLT groups, across any of the examined regions.

These findings support H3, indicating that SD-BOLD, unlike FC, effectively distinguished the control group into high and low memory performers.

V. Discussion

A. Recap of Key Findings

This thesis investigated the relationship between brain functional measures and cognitive performance in relation to CRCI. The main findings showed that resting-state SD-BOLD in the salience network, specifically the left anterior insula, was negatively associated with the executive function and memory. This was found in both continuous correlational analyses and memory-based group comparisons. In contrast, seed-based FC did not show any significant correlations with cognitive performance, nor did it differentiate between high and low memory groups. These results confirm hypothesis 1 and 3, which proposed that higher SD-BOLD would relate to worse cognitive outcomes. However, hypothesis 2, which predicted a positive correlation between hippocampal activity and memory performance, was found to be false. In combination, these findings indicate that SD-BOLD, compared to FC, is a more sensitive measure to detect subtle cognitive alterations, supporting its further implementation in the development of CRCI biomarkers.

B. Comparison with CRCI Literature – Salience Network

It is often reported that breast cancer survivors show disruptions in the SN, a key system that is involved in network switching and cognitive control [2]. The findings of this thesis align with this, as resting-state SD-BOLD in the anterior insula, a central hub in the SN, was associated with cognitive performance [3]. For example, Henneghan and Kesler (2023) found lower SN connectivity in breast cancer survivors compared to healthy controls, as well as that worse executive function was linked to weaker connectivity between the ACC and insula. Our observation complements these findings and further supports the important role of SN in cognitive health, as we found that higher insula variability is linked to worse memory and executive scores. The anterior insula is known to play an important role in the dynamic switching between the DMN and executive control network. Any disruptions in this switching mechanism, whether due to excessive variability or low connectivity, can impair cognitive functioning. By showing that even in healthy individuals, insula variability is linked to memory performance, this thesis reinforces existing CRCI literature, highlighting the SN as a critical network underlying CRCI-related cognitive alteration.

C. Comparison with CRCI Literature – Hippocampus and Default Mode

The hippocampus is a well-known mediator of memory, and past CRCI literature has consistently reported abnormalities in the hippocampal structure and DMN as a result of chemotherapy. For instance, research has reported that cancer survivors experience hippocampal volume loss and reduced DMN connectivity, which are both associated with memory decline [1]. Based on this, we formulated hypothesis 2, stating that in healthy individuals, hippocampal FC correlates positively with memory performance. However, this hypothesis was not supported by the results. No significant associations were observed between hippocampal FC and memory performance (left hippocampus $r \approx 0.24$, $p = 0.20$; right hippocampus $r \approx 0.00$, $p \approx 0.98$), and similarly, FC in other DMN regions such as the lateral parietal cortex and medial prefrontal cortex did not show any correlation with cognition [13].

The difference implies that the hippocampal disruptions reported in CRCI literature are likely pathology-driven, rather than reflecting normal variability in healthy midlife women. This relationship may only emerge under neurobiological stress, such as chemotherapy, rather than regular cognitive aging. This aligns with broader CRCI literature, in which hippocampal and DMN abnormalities, rather than normal aging, are primarily attributed to treatment-induced compensatory mechanisms or neurotoxicity [13]. These results therefore indirectly support CRCI literature by suggesting that the DMN and hippocampal abnormalities observed in patients are more likely caused by treatment rather than natural variability.

D. Functional Connectivity vs. BOLD Variability – Sensitivity to Cognitive Differences

The findings in this thesis show an important difference in FC and SD-BOLD sensitivity. FC, which measures synchrony over time, did not correlate with cognitive performance in the healthy control group. On the other hand, SD-BOLD, capturing fluctuation in neural activity from moment to moment, did show robust negative associations with executive scores and memory, especially in the anterior insula.

One possible explanation for this is that in healthy individuals, FC is relatively stable, specifically in major brain networks such as the SN and DMN. This stability might limit the FC variability range and reduce its ability to reflect an individual's cognitive performance. SD-BOLD, however, is more dynamic and has the ability to reflect short-term fluctuations in neural responsiveness. While some studies have

reported that moderate variability is beneficial for cognition, this thesis found that excessively high insula variability was linked to worse cognitive outcomes. This suggests that in this region, high variability reflects neural instability rather than flexibility, potentially contributing to worse cognitive performance by impairing efficient network switching.

Additionally, changes in FC may emerge only under pathological conditions, such as chemotherapy-induced neurotoxicity. The fact that there is no FC-cognition correlation in healthy individuals might indicate that the connectivity disruptions observed in CRCI literature are not a result of natural variability, but rather reflect therapy-related stress. In combination, these findings support SD-BOLD as a more sensitive and responsive measure to detect subtle or early cognitive changes, specifically compared to static FC metrics, which might need greater pathological disruption to display a measurable effect.

E. Implications for CRCI Biomarkers

The results of this thesis offer important insights for identifying reliable CRCI biomarkers. They suggest that resting-state SD-BOLD in the SN, specifically in the anterior insula, may fulfil the biomarker criteria described earlier more effectively than traditional FC measures. While in this healthy sample no significant FC associations were observed, prior CRCI literature reported changes in connectivity patterns in patient populations, which suggests that under pathological conditions FC may still serve as a biomarker.

Firstly, regarding sensitivity, the insula SD-BOLD measure was able to distinguish subtle cognitive differences in healthy individuals. In this region, participants with lower memory scores showed significantly higher variability, displaying SD-BOLD's sensitivity to even mild cognitive differences. This sensitivity is an important biomarker property, suggesting that at-risk individuals could be identified before more severe deficits emerge, through detection of early subtle impairments. In contrast, FC did not show such sensitivity in our healthy control group, aligning with CRCI literature in which group-level differences in FC were often less robust and modest. This sensitivity offers the potential to detect more pronounced cognitive deficits in cancer survivors, as a good biomarker should detect even mild impairment.

Secondly, regarding specificity, an ideal CRCI biomarker should show brain changes that are specific to cancer and its treatment, instead of general decline related to age or unrelated conditions. Although the SN is implicated in disorders such as PTSD, ADHD and depression, our comparative approach, contrasting healthy controls with CRCI literature, suggests that elevated insula SD-BOLD may be more characteristic of CRCI than of normal aging. In healthy middle-aged women, insula variability was clearly associated with cognitive function. However, survivors report more pronounced disruptions, implying that changes related to treatment might uniquely worsen variability within this region. To confirm this specificity, future studies should compare pre- and post-treatment data in cancer patients.

Thirdly, reproducibility is essential for a clinically useful biomarker. Although this thesis used cross-sectional data, the observed associations were strong and consistent across multiple analyses, suggesting the underlying effect is stable. We applied standardised pre-processing as well as motion correction to minimise potential noise sources. Our results align with prior work showing that certain SD-BOLD metrics can have trait-like stability. Nevertheless, to formally assess generalizability and test-retest reliability across different populations and imaging platforms, further research is needed. In particular, future validation should consider variability related to scanners, as differences in models, analysis pipelines, and data gathering protocols could affect SD-BOLD reproducibility across sites. Applying correction or standardizing imaging protocols are crucial steps to assure SD-BOLD reliability in different clinical settings.

Lastly, the clinical relevance of SD-BOLD within the insula is promising. While fMRI-based metrics are not yet routine in clinical settings, identifying a neural signature such as increased variability in the insula provides a foundational base for objective CRCI assessment. This provides potential to improve diagnosis, guide cognitive interventions, and monitor treatment response. For example, a patient showing high post-treatment insula variability may be flagged for cognitive rehabilitation. Ultimately, combining measures such as inflammatory markers or neuropsychological testing with SD-BOLD might enhance diagnostic precision.

Table V (see Appendix) summarizes the evaluation of FC and SD-BOLD against established biomarker criteria. In summary, this thesis identified that unlike FC, SD-BOLD in the SN, particularly in the left anterior insula , is a sensitive and potentially clinically relevant CRCI biomarker, warranting further validation in patient populations. A next step to identify individuals at risk of CRCI could include piloting SD-BOLD measurement in clinical screening protocols for breast cancer survivors.

F. Subjective Cognition and the Anterior Insula

An interesting interpretation of the findings, regarding the insula is that they go beyond solely cognitive performance. Namely, the anterior insula is not only involved in salience processing, but also plays an important role in the awareness of internal states. Given that CRCI patients often report cognitive impairments even without objective deficits, it is possible that insula dysfunction disrupts self-monitoring of cognitive abilities. In this context, our observed SD-BOLD elevation in the anterior insula may reflect neural instability that affects how individuals feel about their cognition, instead of their actual cognitive performance. The frequent mismatch between subjective complaints and objective test results that is often observed in CRCI, could partially be explained by this. This suggests that biomarkers such as SD-BOLD would not only capture performance-based outcomes, but also perceived impairment. This mechanism could prove to be a crucial neural explanation for the ambiguous diagnosis of CRCI and

has potential to help guide more comprehensive and patient-centred treatments.

G. Limitations

There are, however, some important limitations that should be considered when implementing the findings. First, solely healthy middle-aged women were included in the sample, analysed as a replacement of the cancer survivor population. Although with this approach a well-controlled baseline is formed, without cancer or chemotherapy effects, it does limit the generalizability of the results. Legitimate CRCI patients may experience additional factors, such as emotional stress, hormonal changes, fatigue, or chemotherapy exposure, potentially further influencing brain function. Therefore, substituting direct patient analysis with literature comparison introduces potential bias, as differences in population and study protocols may affect the findings.

Second, the sample size of the healthy control dataset was relatively small (N=31). To address this, we used non-parametric tests and focused on large effect size relationships (e.g., insula, $r \approx -0.6$). However, smaller effects, such as weaker FC–cognition associations, may have gone undetected due to limited statistical power. A larger sample could improve sensitivity for detecting such effects, especially for FC.

Third, the cognitive assessments that were used in this study, especially the SES as a proxy for executive function and the CVLT for verbal memory, captured crucial but limited cognitive domains. The SES was selected as a proxy because of its links with metacognitive processes and its self-regulation, both of which are key components of the executive function. CRCI often involves broader deficits, such as processing speed and attention impairments, both of which were not directly assessed here. It is possible that associations between cognition and FC or SD-BOLD can emerge in one of the cognitive domains that were not included in this analysis.

Fourth, the cross-sectional design used in this thesis prevents causal interpretation [2]. While correlations between cognitive performance and insula variability and connectivity were observed, it is still unclear whether pre-existing neural differences contributed to lower memory scores or whether there is a difference in SN engagement within individuals with weaker memory performance. To validate FC and SD-BOLD as true CRCI biomarkers it is essential to establish whether changes in these measures are causally linked to treatment-induced cognitive decline. To do so, longitudinal data, particularly from cancer patients before and after chemotherapy would be required [13].

Fifth, related to imaging and analysis there were some methodological constraints. Since the anatomical (T1-weighted) scans from the PEARL-Neuro dataset were not publicly available, fMRI analyses were performed in native functional space with no precise normalization. Although standard pre-processing techniques were applied and seed coordinates were carefully selected with the use of prior studies, the absence of full normalization and physiological noise correction, such as RETROICOR, may have affected the FC and SD-BOLD measures' accuracy. For instance, unmodeled physiological fluctuations or less precise insula region placement might have inflated SD-BOLD estimates. To address these concerns, partial smoothing and motion correction were applied, as well as focusing on group comparison (which should affect both groups equally), though registration imprecision and residual noise remain limitations. Additionally, no ICA-based artifact removal or nuisance regression was performed, such as CompCor [23], which may have introduced residual motion or physiological noise.

Sixth, scanner-related variability across datasets has potentially influenced comparability. While no raw imaging data was pooled and each dataset was independently analysed to minimize scanner confounds, differences in scanner models, acquisition parameters, and field strengths across studies could indirectly affect comparability of results.

Seventh, the sample characteristics constrain the generalizability. All participants were women within the age range 50-63, which is an appropriate range for post-chemotherapy breast cancer survivor approximation. However, it may not extend to younger survivors or males with cancer, such as CRCI in testicular cancer. Furthermore, the higher end of cognitive functioning was likely represented by the healthy individuals without cognitive impairments. In contrast, cancer survivors regularly experience fatigue or co-morbidities, which were not captured in this study.

Last, although the thesis aimed to discuss the potential of FC and SD-BOLD as a potential biomarker, no formal diagnostic testing was performed, (e.g., no predictive modeling or receiver operating characteristic curves). As a result, validated classification performance claims regarding specificity and sensitivity remain theoretical and based on statistical significance tests.

Altogether, these limitations accentuate the need for caution when interpreting the findings of this study. Although this study generates testable hypotheses and contributes valuable information, further research including a larger sample size of participants, direct cancer survivors' analyses, and longitudinal designs is required for the validation of FC and SD-BOLD in the insula as clinically useful and reliable CRCI biomarkers.

H. Future Directions

Building on the findings of this thesis, several directions are recommended for future research. Firstly, insula SD-BOLD validation is a priority. Resting-state fMRI data of patients both pre- and post- chemotherapy should be collected in future studies to directly test whether insula variability correlates with cognitive decline [2], as well as whether there is an increase post-treatment. Furthermore, longitudinal designs are required to establish the temporal trajectory of insula SD-BOLD, specifically to evaluate whether variability remains elevated or normalizes over time in patients who continue to experience cognitive difficulties.

However, due to financial and logistical constraints, obtaining longitudinal FMRI-data both before and after chemotherapy may be difficult. To address this limitation, cross-sectional

designs using post-treatment scans can still provide important insights on the association between SD-BOLD and cognitive outcomes, specifically when combined with symptom severity and cognitive assessments.

A crucial next step is to test for possible intervention. If an increase in insula variability results in cognitive difficulties, future studies should investigate whether targeted intervention such as cognitive training, pharmacological treatments, or neuromodulation (e.g., repetitive trans cranial magnetic stimulation targeting the insula or dorsal anterior cingulate cortex) have the potential to reduce insula variability and improve cognitive outcomes.

In line with biomarker development, multiple pharmacological interventions are being examined for CRCI, although currently, none rely on imaging-based biomarkers such as FC and SD-BOLD. For example, Donepezil, often used in Alzheimer's disease, may improve memory and processing speed in brain tumor survivors [24], while Modafinil, a wakefulness-promoting agent, has shown improvements in attention and memory in breast cancer survivors [25]. Furthermore, Metformin has been thoroughly studied in animal models, where it provided promising effects on neurogenesis and cognitive recovery after chemotherapy. Although human research is still limited, early clinical and observational studies suggest potential cognitive benefits, especially in cancer survivors and diabetic patients. [26]. Future studies might examine whether biomarkers such as SD-BOLD help identify patients who may benefit from such interventions, or monitor treatment effects.

It is also essential to expand the range of neural and cognitive measures. This includes cognitive domains such as processing speed, multitasking and attention, alongside more advanced imaging metrics, such as network topology, effective connectivity, or structural connectivity derived from diffusion MRI, which could give a better understanding of brain changes related to CRCI.

Similarly, focusing on developing multimodal biomarkers is important in future research. Combining potential biomarkers such as blood-based inflammatory or hippocampal volume with insula SD-BOLD may improve diagnostic accuracy in addition to what can be achieved by using solely SD-BOLD. It is also necessary to attempt standardizing the SD-BOLD measurement. Multi-centre collaborations to assess the reproducibility of SD-BOLD across different analysis pipelines, scanners, and imaging sites can be used to improve the clinical utility and reliability of the measure.

Lastly, the effect of individual differences such as stress, fatigue, and anxiety on SD-BOLD should be accounted for in future studies. In addition, medications that act on the central nervous system, such as sedatives, antidepressants, and antipsychotics, may influence activity in the resting state and should be taken into account as potential influencing factors. This is an essential step to ensure that any identified biomarker, rather than reflecting physiological distress or broader psychological factors, is specific to cognitive impairment. By addressing these priorities in research, the field can move closer to establishing an objective, clinically useful biomarker for cognitive impairment related to chemotherapy, to improve diagnosis and patient care.

VI. Conclusion

This thesis investigated resting-state FC and SD-BOLD as potential biomarkers for cancer-related cognitive impairment (CRCI). Among the two measures, SD-BOLD in the salience network (SN) emerged as the most promising candidate, successfully distinguishing between high and low memory performers and showing consistent negative associations with executive function and memory scores. In contrast, FC measures, such as hippocampal-DMN connectivity, did not show any significant associations with cognitive performance in the healthy control group. Based on these findings, we conclude that neural variability in key network hubs may be more sensitive to subtle cognitive alterations than static connectivity strength.

In answering **RQ1**, therapy-relevant alterations in resting-state activity were found in this study by analysing the associations between FC and SD-BOLD with cognitive performance. Specifically, strong associations were shown in SD-BOLD, where cognitive relations were observed even in the healthy control group, indicating SD-BOLD is sensitive to subtle brain behaviour relationships.

Regarding **RQ2**, the findings suggest that among the two investigated measures, SD-BOLD, specifically in the anterior insula, has a greater potential to be a CRCI biomarker. This is supported by SD-BOLD's strong overall associations with cognition and a clear ability to differentiate between high and low performers in memory and executive function tasks ($r \approx -0.60$, $p < 0.001$) even within a healthy control group.

For **RQ3**, SD-BOLD in the anterior insula showed significant negative correlations with cognitive scores (memory: $r \approx -0.40$, executive function: $r \approx -0.60$), unlike FC, which did not provide meaningful results. These results strengthen the evidence that the anterior insula is involved in numerous cognitive processes, and highlighting SD-BOLD to be the more robust marker for neural–cognitive relationships observed in this study.

Altogether, SD-BOLD in the anterior insula emerges as a sensitive and potentially useful biomarker for CRCI [13], whereas FC measures were less sensitive and did not capture cognitive differences in the healthy group.

While they are exploratory, the findings in this thesis align with prior CRCI literature and suggest that chemotherapy-related neurobiological stress may contribute to cognitive deficits, resulting in increased network instability. Overall, this work lays a foundation for future research validating insula SD-BOLD in cancer survivors and encourages the development of multimodal biomarkers to improve early detection, intervention, and monitoring of cognitive health in cancer survivors. By advancing understanding of the brain's functional correlates of cognitive change, this study contributes a step forward towards mitigating the cognitive side effects of cancer treatment.

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APPENDIX

The following figures and tables are referenced in the main text and shown here for clarity.

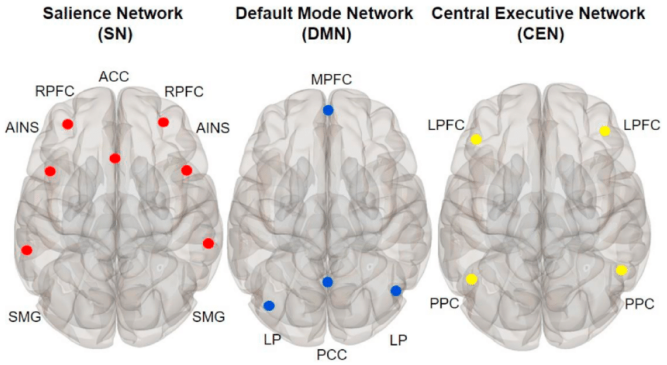

Fig. 1. Overview of core brain regions in the salience network (SN), default mode network (DMN), and central executive network (CEN). Adapted for illustration purposes [21]

TABLE I
SEED REGIONS AND MNI COORDINATES

Network	Region	x	y	z
DMN	mPFC	1	55	–3
DMN	PCC	1	–61	38
DMN	Left LP	–39	–77	33
DMN	Right LP	47	–67	29
SN	ACC	0	22	35
SN	Left AINS	–44	13	1
SN	Right AINS	47	14	0
FPN	Left RPFC	–32	45	27
FPN	Right RPFC	32	46	27
FPN	Left SMG	–60	–39	31
FPN	Right SMG	62	–35	32
Hippocampus	Left Hippocampus	–28	–6	–12
Hippocampus	Right Hippocampus	30	–8	–14

TABLE II
CORRELATION BETWEEN HIPPOCAMPAL FC AND CVLT1 IN HEALTHY CONTROLS

Seed	Score	r	p	FDR
Hippocampus L	CVLT1	0.24	0.20	No
Hippocampus R	CVLT1	≈ 0.00	0.98	No

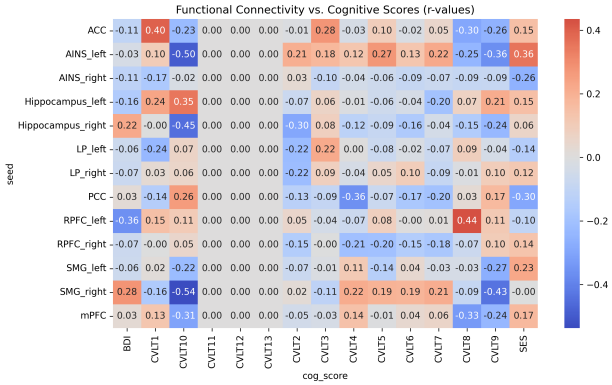

Fig. 2. Heatmap of Seed-Based Functional Connectivity (FC) Correlations with Cognitive Scores. The matrix is a visualization of the correlation coefficients (r-values) between the FC of each selected seed node and all cognitive scores. The warmer (red) colors indicate positive correlations, whereas the cooler (blue) colors represent negative correlations.

TABLE III
GROUP COMPARISON: FC DIFFERENCES BETWEEN HIGH AND LOW CVLT GROUPS (ALL SEED REGIONS)

Seed	t	p	Mean Low	Mean High
Hippocampus_right	0.79	0.43	0.00089	-0.00025
mPFC	0.61	0.55	0.00149	8.40e-05
RPFC_left	0.12	0.90	0.00276	0.00252
AINS_left	-0.20	0.84	0.00021	0.00064
Hippocampus_left	-0.39	0.70	0.00137	0.00190
LP_right	-0.60	0.55	-0.00016	0.00166
LP_left	0.17	0.87	0.00033	0.00012
AINS_right	1.17	0.26	0.00523	0.00197
PCC	-0.13	0.90	0.00220	0.00257
SMG_left	1.11	0.28	0.00134	-0.00137
SMG_right	1.29	0.21	0.00254	-0.00029
RPFC_right	0.08	0.94	0.00221	0.00208
ACC	0.25	0.80	0.00048	0.00231

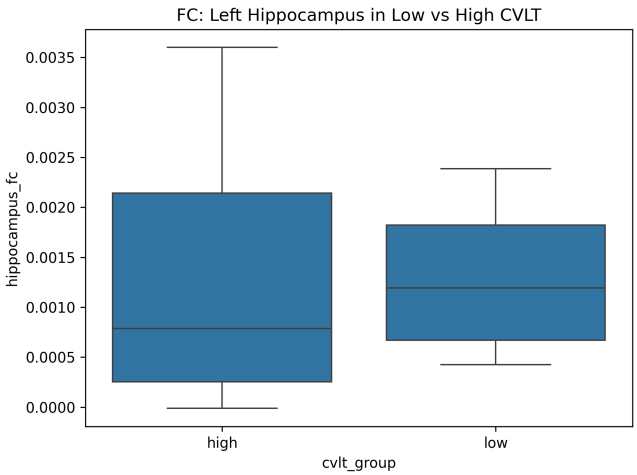

Fig. 3. Left Hippocampus FC in Low vs High CVLT1 Memory Performers. This boxplot compares mean FC values of the left hippocampus groups split based on CVLT1 performance. No significant differences are observed.

TABLE IV
SD-BOLD CORRELATIONS WITH COGNITIVE SCORES IN SALIENCE REGIONS

Region	**Score**	r	p	**FDR**
AINS-L	CVLT1	≈ -0.40	< 0.03	No
AINS-L	SES	≈ -0.60	< 0.001	Yes
AINS-R	SES	≈ -0.59	< 0.001	Yes
ACC	CVLT1	≈ -0.29	≈ 0.12	No

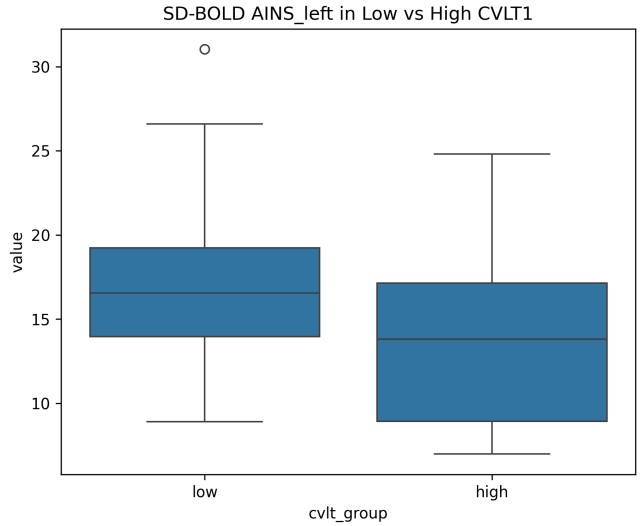

Fig. 4. SD-BOLD in Left Anterior Insula by CVLT1 Memory Group. The boxplot shows a significantly higher SD-BOLD in the low memory group compared to the high-memory group ($p = 0.044$).

TABLE V
COMPARISON OF FC AND SD-BOLD AGAINST BIOMARKER CRITERIA

Measure	**Sensitivity**	**Specificity**	**Reproducibility**	**Clinical Relevance**
SD-BOLD	✓	✓	△	✓
FC	△	△	△	△

✓= supported by findings and literature; △ = partially supported or inconclusive.

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