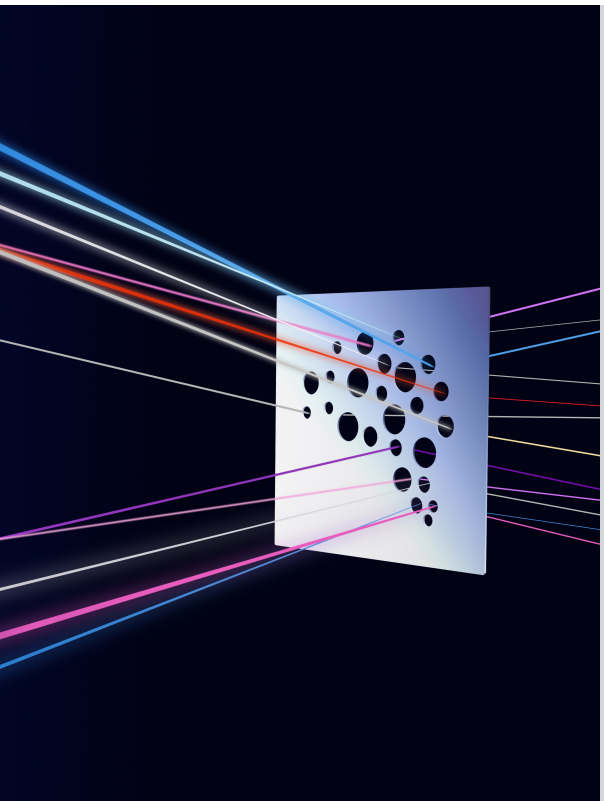
Olink™ Target 48 Neurodegeneration provides insights into the pathophysiology of Parkinson's disease

A collaborative case study performed by Olink Proteomics (part of Thermo Fisher Scientific) and Octave Bioscience, Inc.



Study highlights

- The Olink™ Target 48 Neurodegeneration panel showed high detectability and precision in plasma from Parkinson's disease (PD) participants.
- DOPA decarboxylase (DDC) continues to emerge as a key plasma biomarker for distinguishing PD from healthy controls and tracking participants taking dopaminergic therapies.
- Early disease window (0-5 years after baseline) showed the strongest proteomic changes.
- Strong concordance was observed between Olink Target 48 Neurodegeneration and Olink™ Explore HT.

Background

Parkinson's disease (PD) is a progressive neurodegenerative disorder. PD diagnosis currently depends on clinical presentation, which emerges only after significant neuronal degeneration, and no blood-based tests are yet established for early detection or tracking disease progression.

While most PD cases are sporadic, a subset arises from genetic mutations, with LRRK2 being one of the most common and therapeutically relevant genes. While sporadic and LRRK2-associated PD share many clinical features, whether they differ in biological drivers of disease state or progression rates remains unclear, underscoring the critical need for biomarkers that can provide insights into biology of sporadic- and LRRK2-PD.

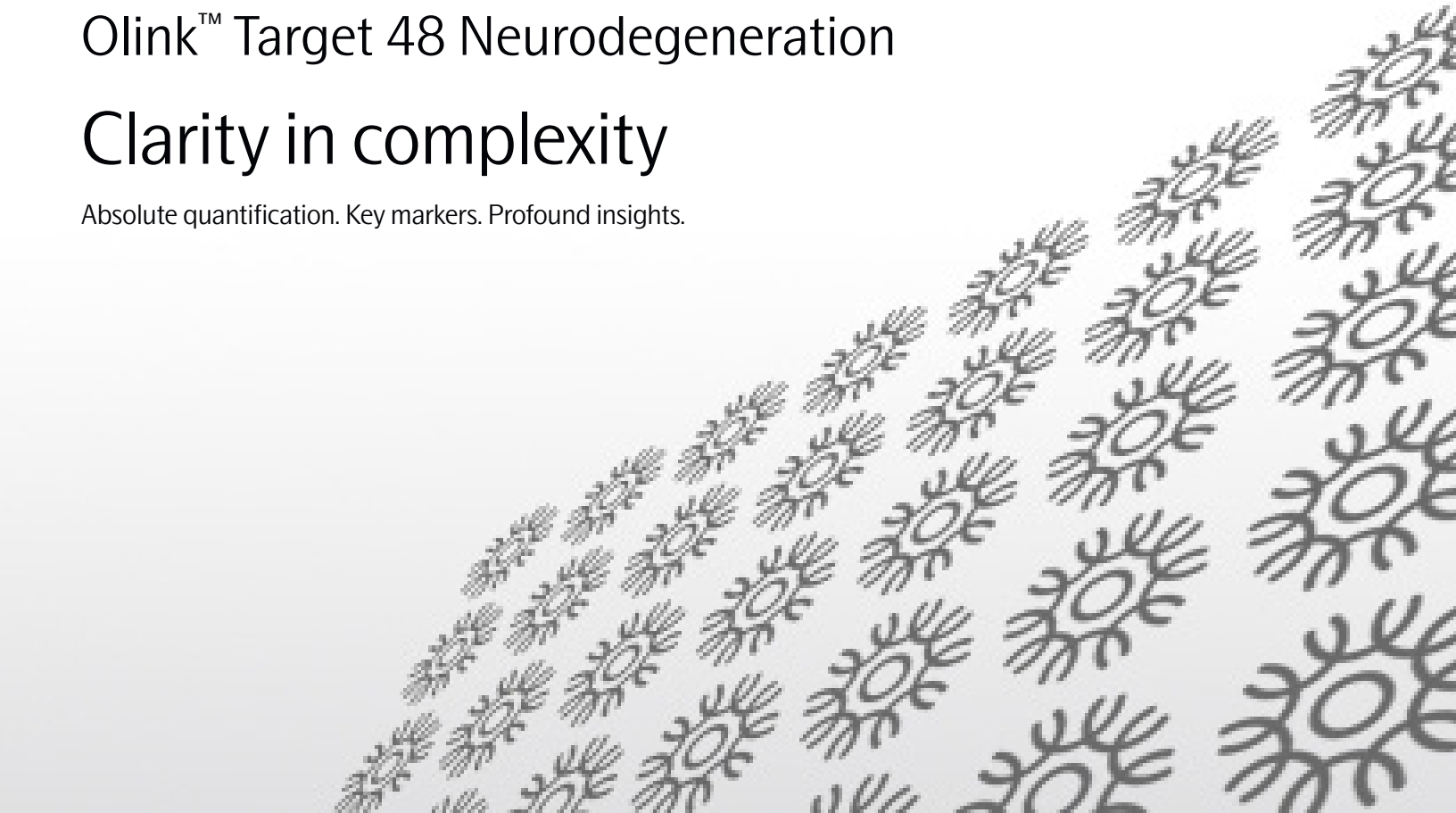
This has driven growing interest in plasma protein biomarkers, which offer a minimally invasive, scalable way to capture molecular changes associated with neurodegeneration, inflammation, and altered signaling pathways relevant to both sporadic and genetic PD.

In this study, Octave Bioscience leveraged the Olink Target 48 Neurodegeneration panel to conduct a pilot study to identify plasma protein biomarker candidates related to neurodegeneration for associations with PD and to longitudinally profile PD participants up to 16 years after diagnosis.

Olink™ Target 48 Neurodegeneration

Clarity in complexity

Absolute quantification. Key markers. Profound insights.



Study aims

1. Compare the absolute levels of 41 neurodegeneration-related proteins across healthy controls, sporadic and LRRK2 PD participants using PEA™ technology.
2. Perform cross-sectional and longitudinal analyses in PD participants up to 16 years after diagnosis.
3. Evaluate correlation for 35 overlapping biomarkers between the Olink Target 48 Neurodegeneration and Olink Explore HT panels.

Study design

Forty-one proteins associated with neurodegeneration (Olink Target 48 Neurodegeneration) were measured in a subset of 357 samples from the **Michael J. Fox Foundation-sponsored Parkinson's Progression Markers Initiative (PPMI)** study, including healthy controls (N=46), sporadic PD (N=45), and LRRK2 PD (N=28) participants (Figure 1) collected at 3 time points: baseline (time of study enrollment; 0-2 years since diagnosis for sporadic PD and 0-7 years since diagnosis for LRRK2 PD), 3-5 years after baseline, and 7-11 years after baseline (Figure 2 and Table). No significant differences in clinical or demographic variables were present between participants in any group at baseline.

Summary detectability statistics and protein expression analyses were performed to interrogate disease-specific profiles.

For up-to-date information on the PPMI study and its funding partners, visit www.ppmi-info.org.

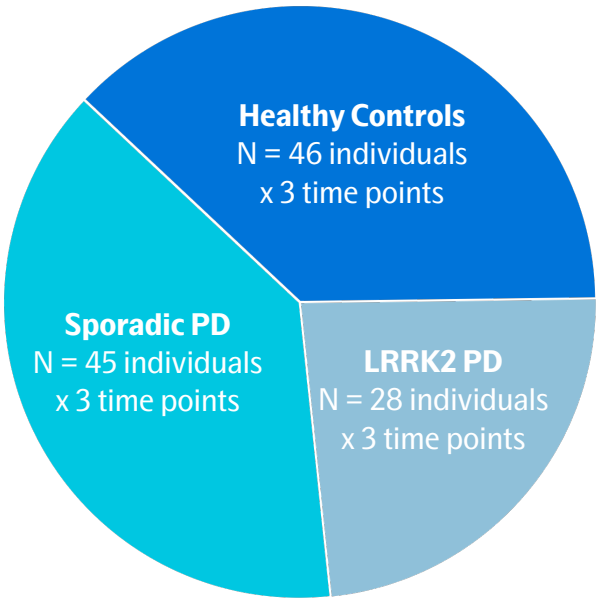


Figure 1. Overview of the study groups included in the analysis.

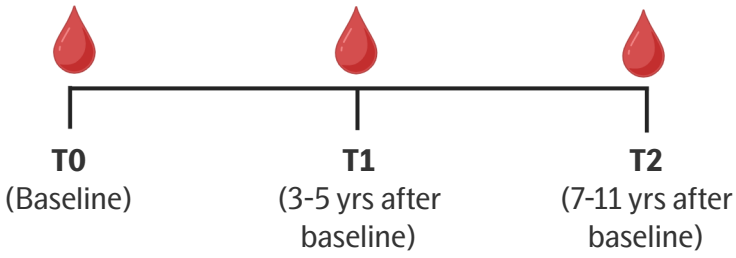


Figure 2. Overview the study design. Plasma was collected at baseline - time of enrollment (T0), 3-5 years after baseline (T1), and 7-11 years after baseline (T2).

Table. Participant demographic and clinical characteristics by group and time point.

Time Point	Group	% Male	Age[a]	Disease Duration[a]	LEDD[b]	N
T0	Healthy Control	59	60.4 (11.6)	NA	0 (0)	46
T0	LRRK2	57	59.7 (9.4)	2.4 (2.1)	471 (419)	28
T0	Sporadic	56	59.6 (11.2)	0.6 (0.5)	0 (0)	45
T1	Healthy Control	59	64.5 (11.7)	NA	0 (0)	46
T1	LRRK2	57	63.6 (9.3)	6.3 (2.2)	850 (504)	28
T1	Sporadic	56	63.4 (11.1)	4.4 (0.6)	427 (241)	45
T2	Healthy Control	59	68.8 (11.6)	NA	0 (0)	46
T2	LRRK2	57	68.1 (9.3)	10.8 (2.5)	1221 (1419)	28
T2	Sporadic	56	68.3 (11.0)	9.3 (1.1)	811 (501)	45

[a]Reported as the mean and standard deviation (years).

[b]Levodopa equivalent daily dose; reported as the mean and standard deviation (mg/day).

Results

High protein detectability in Parkinson's disease plasma

All samples passed quality control with no observable differences detected via principal component analysis, either based on study group or follow-up time (Figure 3).

High levels of detectability were observed across all samples and study groups. All 41 proteins were detected in at least one sample, while 39 proteins were detected in >50% of samples and 37 proteins were detected in >80% of samples.

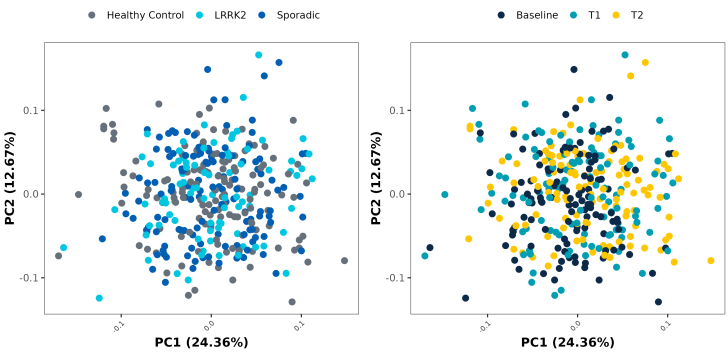


Figure 3. Principal component analysis of all samples based on (left) study group and (right) follow up time point.

Cross-sectional analyses identified proteomic differences between Parkinson's disease participants and healthy controls

Cross-sectional analyses of all 41 proteins identified DOPA decarboxylase (DDC) as differentially expressed in PD participants when comparing sporadic and LRRK2 PD groups to healthy controls at baseline and T2, the initial and terminal timepoints included in this analysis. DDC was significantly higher in LRRK2 PD participants at baseline and T2, while DDC was significantly elevated in sporadic participants at T2, compared to healthy controls. The discrepancy between LRRK2 and sporadic PD is likely explained by the use of dopaminergic therapy at baseline amongst LRRK2 PD participants versus no dopaminergic therapy at baseline in sporadic PD participants at baseline.

Multivariate analysis of variance (MANOVA) using Pillai's Trace was also performed across all samples to assess overall group differences in PD participants compared to healthy controls (Figure 4). Those analyses revealed that DDC levels were higher in PD cases taking dopaminergic therapy, while NEFL, BMP7 and TP53 exhibited nominal differences.

Subgroup analyses comparing sporadic and LRRK2-associated PD via generalized least squares with LEDD as a covariate revealed significantly lower GFAP levels in LRRK2 cases. Conversely, DDC levels were nominally elevated in the LRRK2 cohort, though these elevations may be influenced by differences in disease duration and dopaminergic therapy (Figure 4).

Those findings are consistent with prior studies in the same samples using Olink Explore HT and provide insights

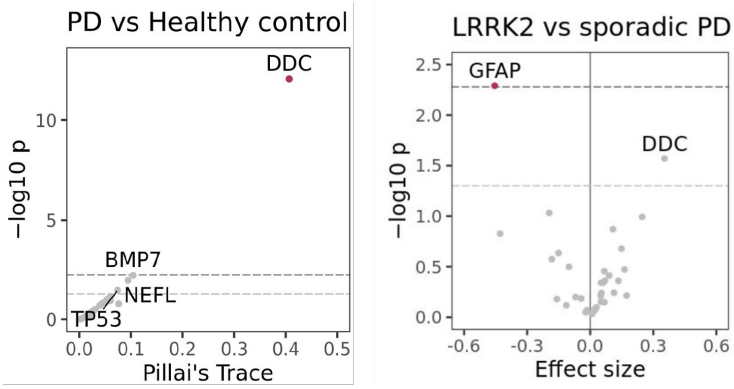


Figure 4. MANOVA using Pillai's Trace across all samples included in the study, comparing PD vs healthy samples (left) and generalized least squares regression on protein levels from LRRK2 vs sporadic PD samples (right).

into the differences in expression between PD participants and healthy controls, as well as between sporadic and LRRK2 PD participants. The finding that plasma GFAP was lower in LRRK2-associated PD than in sporadic PD may be reflective of lower astrocyte activation in LRRK2 participants, resulting in less GFAP being released into blood. However, the potential confounding effect of longer disease duration in this subgroup must also be considered. Those data also support recent findings suggesting GFAP is a potential marker of PD disease progression and the interpretation of subgroup differences (1).

Longitudinal analyses reveal time-dependent proteomic changes in Parkinson's disease

To capture temporal changes in protein expression across the three timepoints, linear mixed-effects modeling was initially applied with age and sex included as covariates. Longitudinal analyses within PD subgroups identified several proteins with significant changes over time, while no longitudinal differences were observed in healthy controls.

In the sporadic PD group, six proteins—DDC, WWOX, EIF2AK2, TP53, DDAH1, and FOXO3—showed significant longitudinal changes. To account for potential confounding by dopaminergic treatment, LEDD was included as an additional covariate. After adjustment, three proteins—WWOX, EIF2AK2, and FOXO3—remained significant, while DDC, TP53, and DDAH1 showed nominal significance (adjusted p = 0.07-0.09) (Figure 5).

Significant expression changes were observed primarily between baseline and T1 but not between T1 and T2. Those results indicate that proteomic changes are most pronounced within the first five years following diagnosis, after which expression levels plateaued.

DDC was also significantly elevated in the LRRK2 group between baseline and T1, but not between T1 and T2, even after adjusting for LEDD. This further supports the observation that protein expression peaks within several years of diagnosis before stabilizing (Figure 6).

DDC has emerged as a promising biofluid marker of endogenous dopamine deficits, with peripheral circulating levels correlating with disease severity and longitudinal motor decline. While these findings are interesting the association of plasma DDC level with dopaminergic therapy precludes its utility as a marker of disease progression (2).

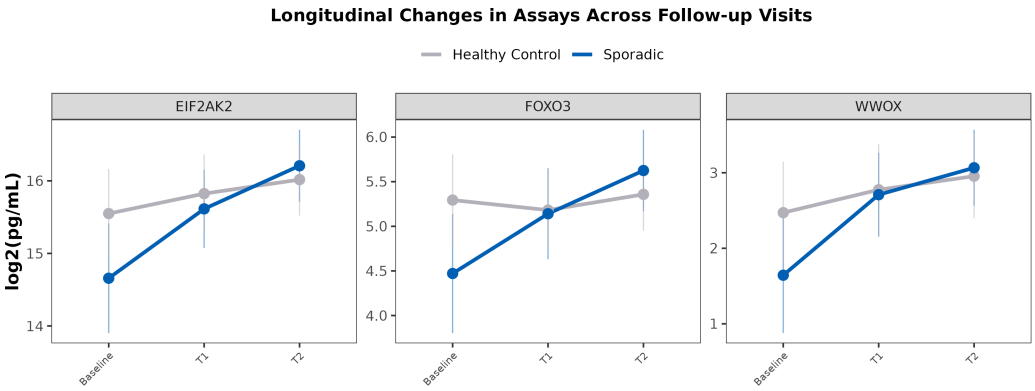


Figure 5. Longitudinal changes in protein expression in sporadic PD participants. Data shown for three significantly differentially expressed proteins.

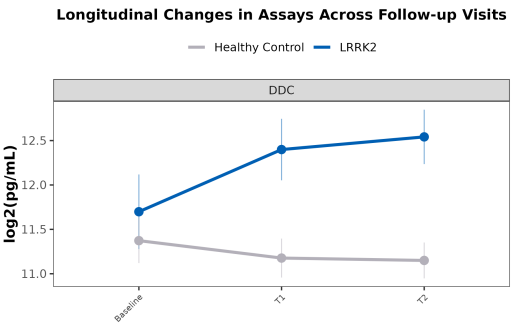


Figure 6. Longitudinal changes in DDC expression in LRRK2 PD participants.

Similarly, EIF2AK2 is increasingly considered an emerging blood-based marker of PD–related biology and changes in circulating EIF2AK2 may reflect systemic stress and inflammatory processes associated with disease progression (3).

Strong correlation between Olink Target 48 Neurodegeneration and Olink Explore HT

Cross-sectional findings were consistent with results from prior analyses of the same samples using Olink Explore HT. Thirty-five proteins overlap between Olink Target 48 Neurodegeneration and Olink Explore HT panels. Overlapping proteins measured in matched samples demonstrated strong Pearson correlation coefficients, with 30 proteins showing significant correlations, the majority of which exceeded r = 0.6 (Figure 7).

Those data highlight the consistent analytical performance between panels, likely attributable to the shared PEA technology, and demonstrate the advantages of using a unified technology when scaling biomarker analyses. For additional discussion on scaling PEA™-based studies, see references on bridge normalization strategies and data analysis (4, 5).

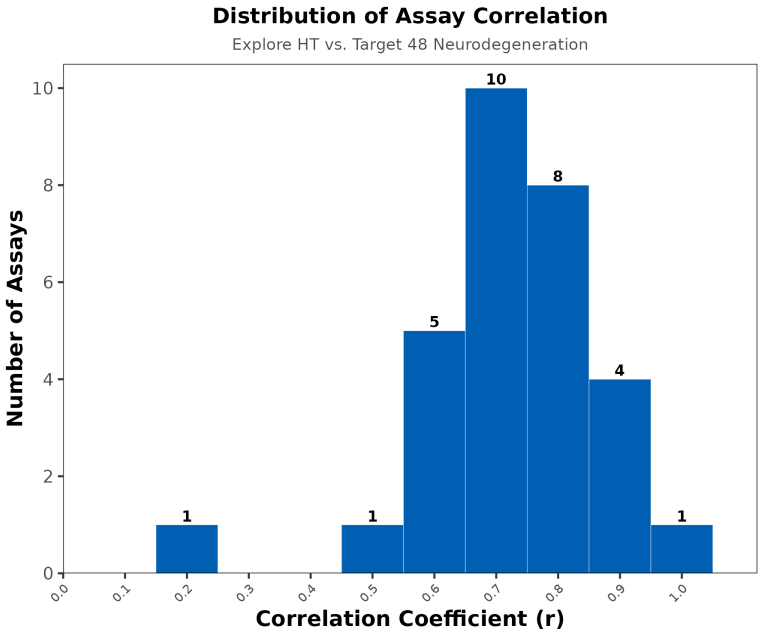


Figure 7. Histogram of Pearson correlation coefficient (r) distribution between Olink Target 48 Neurodegeneration and Olink Explore HT in matched samples. The r values were computed for overlapping proteins using NPX values above the limit of detection in both platforms. Data are for 30 of 35 proteins showing significant correlations.

Conclusions

Using the Olink Target 48 Neurodegeneration panel, this study identified plasma proteins that are differentially expressed both cross-sectionally and longitudinally in PD, providing insight into disease state, subtype-specific biology, and progression over time.

Several proteins, including DOPA decarboxylase (DDC), exhibited consistent changes across sporadic and LRRK2-associated PD, with the most pronounced proteomic shifts occurring within the first five years following enrollment. This early disease window may be particularly informative for participant stratification and therapeutic intervention.

This work demonstrates the strong analytical performance and translational utility of the Olink platform for neurodegeneration research. The Olink Target 48 Neurodegeneration panel exhibited high detectability, precision, and robustness in plasma samples, enabling reliable measurement of low-abundance, disease-relevant proteins using a minimally invasive approach.

Olink Target 48 Neurodegeneration complements other Olink panels, such as Olink Explore HT by providing absolute quantification of key proteins, while uniquely enabling measurement of critical neurodegenerative markers such as pTau217, Aβ40, Aβ42, LRRK2, TREM1, and NGF.

The strong concordance observed between Olink Target 48 Neurodegeneration and Olink Explore HT underscores the scalability of Olink PEA™ technology and its ability to support both targeted and high-content proteomic analyses while maintaining data continuity.

Collectively, these findings highlight the value of Olink-based proteomics as a flexible approach for biomarker discovery and longitudinal disease monitoring in PD. By combining high sensitivity, reproducibility, and cross-platform consistency, the platform enables efficient identification and scaling of protein biomarkers that capture disease heterogeneity and temporal dynamics.

"Using the Olink™ Target 48 Neurodegeneration panel in our Parkinson's disease research allowed us to interrogate key neurodegenerative pathways with a level of sensitivity and reproducibility that is difficult to achieve in plasma. The panel captured biologically meaningful changes in proteins across sporadic and LRRK2 PD participants and is a powerful tool for studying PD pathophysiology"

Ferhan Qureshi, SVP Biomarker R&D, Octave Bioscience, Inc.

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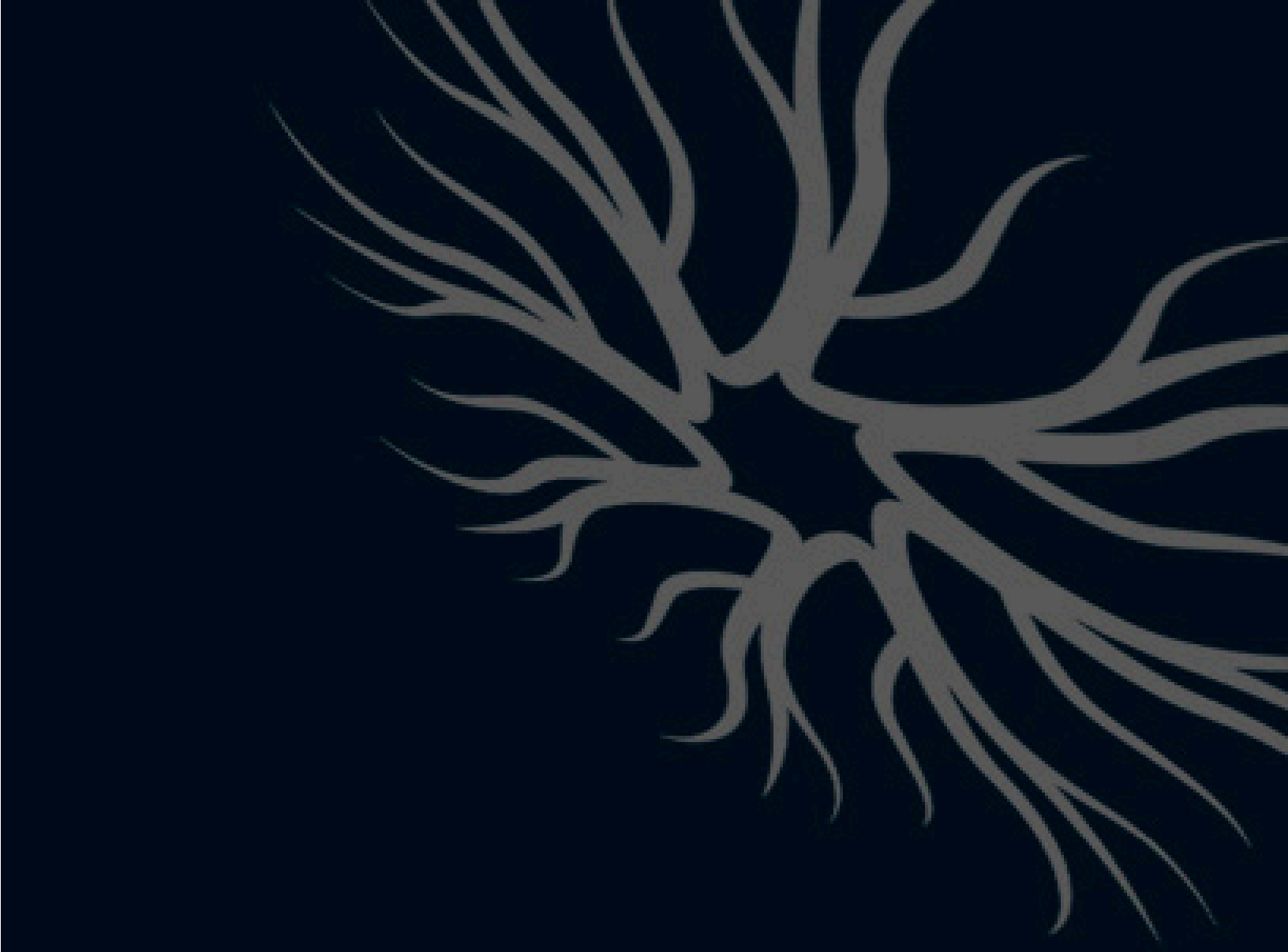

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