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Electrophysiological Measure of Impaired Information Processing in Drivers with Hematological Malignancy

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Abstract

The broad goal of this study is to measure remote effects of cancer on brain physiology and behaviors that underpin instrumental activities of daily living such as automobile driving. Studies of hematological malignancies (HM) have demonstrated impairments in multiple brain functions shown to be critical for safe automobile driving. In the current pilot study, brain physiology during driving simulation was examined in 14 HM patients and 13 healthy comparison drivers. Electroencephalography was used to measure the eye fixation-related potential (EFRP)—a positive amplitude deflection evoked approximately 100 milliseconds after eye movement termination. Previous studies have demonstrated sensitivity of EFRP activity to information-processing capacity. All drivers completed visual search tasks to evaluate the relationship between driving-related changes in performance and EFRP activity. Results showed smaller EFRP amplitudes in drivers who had: (1) greater driving-related changes in visual search performance ($p = 0.03$, Cohen's $d = 0.91$); and (2) HM diagnosis ($p = 0.18$, Cohen's $d = 0.54$). Extending previous studies, these results provide neural evidence of reduced information-processing capacity associated with cancer diagnosis. Future large-scale studies are needed to confirm these results, given the high level of uncertainty and small sample size. This study provides a novel platform for linking changes in brain physiology and safety-critical driving behaviors.

Cancer, the “emperor of all maladies,” comprises a range of conditions that affects nearly 0.5% of the U.S. population each year (1). Advances in treatment aim to reduce cancer mortality, and survivors commonly experience long-term quality-of-life impairments (2–4). Multiple studies demonstrate cognitive impairment before treatment (5–11) and potential worsening after chemotherapy (6–9, 12–16). Neuroimaging studies show associated changes

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Author Contributions

The authors confirm contribution to the paper as follows: study conception and design: D.E.A., V.R.B., M.R.; data collection: D.E.A.; analysis and interpretation of results: D.E.A., K.S., M.R.; draft manuscript preparation: D.E.A. All authors reviewed the results and approved the final version of the manuscript.

to brain structure and function (12, 14, 16–19). These results suggest cognitive impairment in cancer survivors is related to a combination of cancer- and treatment-related toxicities.

The overarching goal of the current work is to measure how cancer-related toxicity affects brain physiology and behaviors that underpin instrumental activities of daily living such as automobile driving. Insights into potential links between cancer-related toxicity and driving performance come from investigations of medical disorders and aging. For example, aging (20, 21) and age-related disorders such as dementia (22–25) and glaucoma (26, 27) are associated with poor driving performance and increased risk for motor vehicle crashes. Impaired visual attention is thought to play a key role in at-risk driving in these cohorts (28).

Visual attention is commonly measured using eye-tracking methods and visual psychophysics to understand its role in driving performance (29–35). Saccadic behaviors, including fixation frequency, duration, and variability, are recorded to estimate the locus and control of overt visual attention. When viewing high-density traffic scenes, drivers exhibit greater fixation variability and shorter fixation duration (31). Multiple studies have demonstrated experience-dependent differences in saccadic behaviors (30–32). More experienced drivers show shorter fixation durations (31) and greater fixation variability (30) than novice drivers while viewing complex traffic scenes. Saccadic behaviors also depend on concurrent cognitive load (29, 31, 33–35). Drivers show lower fixation frequency, longer fixation durations, and lower fixation variability when viewing dangerous scenes (31) or completing a secondary attention task (29). Together, these studies suggest inexperience and cognitive load are associated with similar changes to overt attention while driving.

Eye-tracking studies are essential to studying the relationship between saccadic eye movement patterns and driving performance. Critically, however, the spatial loci of fixation and attention may differ (36–38), as is the case of “looking but not seeing.” Electroencephalography (EEG) can provide information on brain activity associated with attention that complements saccadic eye movement patterns. Eye fixation-related potentials (EFRP) are evoked in EEG signals immediately following saccade termination (39–42). The P1 response is a prominent positive deflection in EFRP amplitude approximately 100 milliseconds after saccade termination and has been localized to visual cortex (42, 43). P1 amplitude is associated with accuracy during a proof-reading task (44) and task engagement (45), suggesting EFRPs reflect information-processing mechanisms in sensory and attentional networks.

Few studies have examined EFRP activity in the context of driving (46–48). Takeda et al. measured EFRPs in a simulated environment while drivers performed a verbal or spatial working memory task (46). Increasing cognitive load in the verbal and spatial conditions led to a reduction in saccade frequency, consistent with previous studies (34). Only spatial cognitive load affected P1 amplitudes, suggesting fewer resources were available for visual information processing under a concurrent visual load. Kamienkowski et al. demonstrated comparable spatiotemporal EEG profiles of stimulus-evoked potentials and EFRPs (42), but found that early evoked activity in extrastriate cortex distinguished between target and distractor items only in EFRPs. Similar spatiotemporal EEG profiles were found in a driving

simulation study (49), suggesting EFRPs can provide a window on driver visual attention when eye fixation and attention loci differ.

The current study used state-of-the-art driving simulation, eye movement, and EEG measures to test the hypothesis that visual attention is impaired in cancer patients diagnosed with hematological malignancy (HM), including myelodysplastic syndrome, non-Hodgkin lymphoma, and multiple myeloma. A few EEG studies have demonstrated chemotherapy-related reductions in stimulus-evoked measure of information processing up to 6 years post-treatment in breast cancer patients (50–53). It is currently unknown whether similar EEG measures are affected in HM patients with putative attention impairments (54–56). Consequently, the study measured visual search performance, eye movement behavior, and EFRP activity to investigate visual attention in a group of HM patients who received either chemotherapy or best supportive care. It is hypothesized that information-processing mechanisms of visual attention are impaired in HM relative to comparisons without cancer, as indexed by reduction in EFRP activity.

Methods

Subjects

Participants included cancer patients diagnosed with a hematological malignancy (HM; $n = 30$) and a comparison group without cancer (HC; $n = 15$). HM patients were recruited from University of Nebraska Medical Center (UNMC) Fred & Pamela Buffett Cancer Center. Demographically matched HC participants were recruited from an existing research registry in the UNMC Department of Neurological Sciences. Inclusion criteria for both groups were: (1) age 19–80 years, and (2) normal or corrected-to-normal vision. Exclusion criteria for both groups were: (1) previous cancer diagnosis, and (2) previous radiotherapy or chemotherapy. All participants provided informed consent approved by the UNMC Institutional Review Board and Scientific Review Committee.

Driving Simulator

SENSEI (Simulator for Ergonomics, Neuroscience, Safety Engineering and Innovation; Figure 1a), a DriveSafety (Salt Lake City, UT) RS-600 Research Simulator, provided the driving environment. SENSEI is constructed around a full-sized automotive cab (2004 Ford Focus). SENSEI's cab is centered within 7 Ultra-HD (3840×2160) curved LED displays that provide a 290-degree panoramic field of view. Additional side and center rear-view LCD monitors provide a full 360-degree simulated environment. SENSEI is fully integrated with instrumentation for recording vehicle and driver performance measures.

Driving Scenario

Scenarios were created in HyperDrive Authoring Suite (DriveSafety). Drivers completed a baseline drive on a rural road (5.6 km; 88.5 km/h speed limit) as part of a longer driving simulation study. Drivers were instructed to drive as they would normally. No other task demands were imposed during the baseline drive. Simulator adaptation was implemented prior to driving simulation to prevent simulator sickness; simulator adaptation involved

driving through a suburban roadway (1.95 km; 40.2 km/h speed limit) and stopping at a total of four 4-way intersections.

Overall, drivers completed three secondary tasks in addition to baseline driving. First, drivers completed a baseline visual search task (Task 1; see [Visual Search Task and Procedures](#)). Drivers were then presented with the suburban roadway and completed simulator adaptation. Following simulator adaptation, drivers transitioned onto a rural road. As vehicle speed approached the speed limit (88.5 km/h), drivers completed the visual search task while maintaining vehicle speed and lane position (Task 2). Upon completing the visual search task, drivers completed the baseline drive. Finally, drivers completed a car-following task that required maintaining a two car-length distance behind a lead vehicle whose speed pseudo-randomly fluctuated around 88.5 km/h (Task 3).

Visual Search Task and Procedures

The visual search task required drivers to respond with the identity of a red target Landolt square stimulus presented among black distractor Landolt square stimuli. Stimulus configurations are depicted in Figure 1b. Eight square placeholders (diameter = 2.0° visual angle) were rendered in white and presented around an imaginary concentric circle (radius = 7.3°) centered over a 0.8° white fixation dot. Each placeholder location was separated by 45° , starting at 22.5° and ending at 337.5° . Landolt square stimuli (diameter = 1.7°) were rendered with line thickness of 0.2° and a 0.6° gap centered on one side. Each stimulus display comprised 7 black distractor Landolt squares and 1 red target Landolt square. Distractor squares were rendered in black with the gap on any one side of a given square, and target squares were rendered in red with the gap on either the left or right side of the square. Driver head position was approximately 2.74 m from the central stimulus display.

Each trial started with the presentation of the square placeholders to cue trial initiation. Following a 50-ms cueing period, the stimulus display was presented until a response was made. Drivers were instructed to indicate whether the gap was on the left or right side of the target square by pressing the left or right steering wheel button, respectively. Following each response, placeholder and stimulus displays were removed for an inter-stimulus interval period randomly sampled with replacement from values ranging between 1 and 3 seconds in increments of 1/60th of a second. Target position and target direction were counterbalanced across a total of 48 trials.

Drivers completed the visual search task under two conditions: stationary (low load) and driving (high load). In the stationary condition, visual search displays were presented against a black background and central fixation was visible; in the driving condition, visual search displays were presented against the naturalistic background (Figure 1b) while drivers traveled along a straight rural road.

EEG Recordings

EEG was recorded using a NeuroScan NuAmps (Compumedics) digital amplifier and silver-chloride electrodes distributed in a fitted elastic cap according to the International 10–20 System. EEG was measured from 8 scalp locations (O1, O2, PO1, PO2, P3, P4, P7, P8) with a ground reference electrode at the AFz site. Electrooculography (EOG) was recorded for

both horizontal (HEOG) and vertical (VEOG) eye movements; HEOG was recorded from electrodes placed 1 cm outside the lateral canthus of each eye, and VEOG was recorded from electrodes placed above and below the left eye. Impedances of all electrodes were maintained below 10 k Ω . EEG signals were digitized at a sampling rate of 1000 Hz and re-referenced offline to mathematically averaged left and right mastoids (A1–A2).

Data Analysis

Visual Search Performance.—Visual search performance was estimated as the mean response time across all analyzed trials. Behavioral costs associated with an additional driving load were estimated as the difference between visual search performance in baseline and driving conditions. Incorrect trials and response times >4 s were excluded from analysis.

EFRP.—The primary goal of the current work was to measure differences between HM patients and HC comparisons in a neural correlate of information processing during naturalistic viewing conditions. To this end, EFRPs were measured during driving simulation with unconstrained eye movements. The P1 EFRP component, a positive amplitude deflection approximately 100 ms after saccade offset, was studied. EFRP waveforms were measured from EEG recordings during baseline driving using the following methods.

EEG was analyzed using EEGLab (57) and custom MATLAB scripts. EEG recordings were high (0.01 Hz)-and low (30 Hz)-pass filtered using a 2nd order Butterworth filter. EEG recordings were then extracted 3–240 s after the driving visual search task (Task 2) was completed. HEOG recordings were used to measure eye movements. Saccade offset events were created for timepoints meeting all of the following criteria: (1) for 30 ms of HEOG activity preceding time t , R^2 and β parameter of best fitted regression line were >0.9 and 2.0 uV/ms, respectively; (2) for 150 ms of HEOG activity after time t , root mean squared of residuals and β parameter of best fitted regression line were <20 and 2.0 uV/ms, respectively; (3) difference between β parameters for both regression lines were >2.0 uV/ms.

EFRP epochs were extracted 0–400 ms after each saccade offset event with a 100-ms baseline period. Saccade amplitude was estimated as the absolute difference between HEOG activity observed –150 to –100 ms prior to and 0–50 ms following saccade offset events (47). Individual waveforms were analyzed only for epochs with saccade amplitudes within the range of 100–400 μ V (47) and EEG peak-to-peak amplitudes <160 μ V. P1 amplitudes were measured from O1 and O2 electrodes by averaging EFRP activity $\pm$ 50 ms relative to peak amplitude observed 80–120 ms after saccade offset.

Statistical Analysis.—Statistical analyses were performed with SAS Studio 3.6 (SAS Institute Inc.) using PROC FREQ to analyze categorical data and PROC TTEST to analyze numerical data. Numeric data were descriptively summarized using means and standard deviations, and categorical data were descriptively summarized using frequencies and percentages. Between-group effects on categorical data were assessed using chi-square statistics, between-group effects on numerical data were assessed using independent sample t -tests, and within-group effects on numerical visual search data were assessed using dependent sample t -tests. Odds ratios were used to assess the odds of HM patients showing

worse outcomes (based on median-split) than HC comparisons in visual search and EFRP measures. Cohen's d was used to estimate standardized effect sizes.

Results

Study Enrollment

Forty-five study participants were enrolled in the study at the time of analysis. Of enrolled participants, 17 participants did not complete study procedures for the following reasons: simulator discomfort ($n = 4$), dropped out prior to initiating study procedures ($n = 2$), acute leukemia patients who could not be transported to the driving simulator ($n = 4$), technical difficulties with EEG ($n = 1$), research assistant error ($n = 1$), patient not wearing EEG during driving simulation ($n = 1$), or ongoing study participation ($n = 4$).

Of the 17 participants who did not perform the current study, 88% were HM patients ($n = 15$) and 12% were HC participants ($n = 2$). Of the 15 HM patients who did not perform the current study, 60% were receiving chemotherapy ($n = 9$) and 40% were receiving best supportive care ($n = 6$).

Study Patient Characteristics

One HM patient was excluded from analysis because of anisometropia, resulting in 14 HM patients and 13 HC comparisons that were included in the current study. HM patients were diagnosed with myelodysplastic syndrome ($n = 4$), non-Hodgkin lymphoma ($n = 9$), or multiple myeloma ($n = 1$). Of the 14 HM patients that completed task procedures, six were receiving chemotherapy and eight were receiving best supportive care. HM and HC groups did not differ along demographic dimensions of gender (HM: 50% female; HC: 46% female; $\chi^2 = 0.04$, $p = 0.84$), age (HM: 61.6 ± 14.0 ; HC: 58.0 ± 17.0 ; $t_{25} = 0.61$, $p = 0.55$), or years of education (HM: 13.8 ± 1.8 ; HC: 14.4 ± 1.7 ; $t_{25} = 0.90$, $p = 0.38$).

Task Performance

Visual search performance was faster during baseline (989 ± 302 ms) compared with driving (1027 ± 316 ms) conditions ($t_{26} = 1.79$, $p = 0.08$). HM and HC groups demonstrated comparable visual search performances in both baseline (HM = 1055 ± 380 , HC = 917 ± 173 ; $t_{25} = 1.20$, $p = 0.24$) and driving (HM = 1105 ± 386 , HC = 945 ± 56 ; $t_{25} = 1.33$, $p = 0.20$) conditions. Driving load-dependent differences in response times did not differ between HM (49 ± 131 ms) and HC (28 ± 94 ms) groups ($t_{25} = 0.48$, $p = 0.64$). Although between-group differences failed to reach statistical significance, odds of HM patients to show larger load-dependent differences in response times were 2.9 (CI 0.60–13.7) times the odds of HC patients.

Saccade Behavior

Previous EFRP studies have shown P1 amplitudes are more reliable following larger saccades (47). Therefore, saccade events were submitted for analysis only if they fell within the amplitude range of 100–400 μ V. HM and HC groups did not differ from each other in either total number of saccade events (HM: 148.4 ± 97.1 ; HC: 158.1 ± 111.4 ; $t_{25} = 0.24$, $p = 0.81$) or average saccade amplitude (HM: 179.0 ± 16.8 μ V; HC: 183.5 ± 22.0 μ V; $t_{25} = 0.61$,

$p = 0.55$). These results are suggestive of similar saccadic behaviors between HM and HC groups.

EFRP

Grand-averaged EFRP waveforms for HM and HC groups are depicted in Figure 2a. Both groups demonstrated a clear positive deflection in EFRP amplitude in O1/O2 electrodes approximately 101 ms after saccade offset consistent with P1 component. Average P1 amplitudes were larger for HC ($2.51 \pm 1.60 \mu\text{V}$) compared with HM ($1.43 \pm 2.37 \mu\text{V}$) groups ($t_{25} = 1.37$, $p = 0.18$; Cohen's $d = 0.54$; Figure 2c). Using a median-split of P1 amplitudes to partition individual drivers into high or low-amplitude groups, odds of HM patients being in the low-amplitude group were 4.1 (CI 0.81–20.2) times to the odds of HC participants being in the low-amplitude group. These results suggest the capacity of information processing following saccadic eye movements is reduced in HM patients compared with HC participants.

Slower response times during visual search tasks have important implications for detecting hazardous events. Next, the relationship between post-saccadic information processing and behavioral costs sustained in visual search performance completed during driving relative to baseline performance was examined. Using a mediansplit of response time differences, different EFRP patterns were noted between drivers showing low and high costs (Figure 2b). During the P1 window, larger amplitudes were observed in the drivers sustaining smaller behavioral costs ($r = -0.44$, $p = 0.022$). P1 amplitudes were larger for the low-cost group ($2.85 \pm 1.95 \mu\text{V}$) compared with the high-cost group ($1.11 \pm 1.87 \mu\text{V}$; $t_{25} = 2.37$, $p = 0.03$; Cohen's $d = 0.91$). Indeed, odds of low-cost drivers showing larger P1 amplitudes were 20.2 (CI 2.80–144.93; $\chi^2 = 10.8$, $p = 0.001$) times the odds of high-cost drivers, suggesting lower P1 amplitudes may be associated with greater sensitivity to cognitive load on visual search behavior.

Next, the relationship between behavioral costs and P1 amplitudes was examined separately for HM and HC groups. It was found that the odds of low-cost drivers showing larger P1 amplitudes were 31.9 (OR 1.6–666.7; $\chi^2 = 6.64$, $p = 0.01$) and 10.5 (OR 0.67–163.9; $\chi^2 = 3.26$, $p = 0.07$) times the odds of high-cost drivers in HM and HC groups, respectively. These results demonstrate post-saccade information-processing capacity is similarly reduced across groups for drivers slower to detect targets within visual search displays.

Discussion

HM patients are at risk for impaired processing speed and attention (54–56), and impaired visual attention contributes to increased risk for vehicle crashes (28). Consequently, this pilot study used state-of-the-art driving simulation and EEG to test the hypothesis that visual attention is impaired in cancer patients with HM. EFRP activity, an electrophysiological measure of information processing (39–41, 43), showed promising evidence for reduced information processing in HM patients within 150 milliseconds of saccade termination. Amplitudes of the P1 EFRP component were reduced in HM compared with HC drivers. In contrast, HM and HC groups did not differ in saccade frequency or saccade magnitude.

Thus, HM patients differed from HC comparisons in neural information processing and not in saccade measures.

A relationship was also found between driving load-dependent declines in visual search performance and P1 amplitudes (Figure 2b, and d). Previous studies show that older drivers are slower to respond and use more eye movements during visual search within traffic scenes (58). Patients with glaucoma, an age-related eye disease characterized by peripheral visual field loss, are slower to respond and deploy less efficient eye movements during visual search (59). These behavioral patterns may reflect recruited auxiliary mechanisms to compensate for reduced information-processing capacity in posterior cortex (60). In the context of studies demonstrating age- and disease-related changes in visual search performance (58, 59), increased saccade frequency may be an auxiliary mechanism for overcoming reduced neural information-processing capacity by sampling driving scenes more frequently and consequently boosting signal-to-noise ratio. The current work shows reduced neural information-processing capacity (i.e., P1 amplitudes) in drivers showing greater load-dependent declines in visual search performance, which was more prevalent in HM drivers. These findings promote further investigations to elucidate the relationship between reduced neural information-processing capacity and saccade behavior in HM patients during more complex visual search scenes.

Spatial loci of fixation and attentional resources were found to be separable. This recalls the situation of inattention blindness, (61, 62) in which observers fail to detect an unexpected object within the locus of fixation (61, 63). These findings militate against exclusive reliance on eye-tracking methods to study visual attention. Further investigation is needed on relationships between disease-related changes in saccade behavior and information-processing metrics in visual cortex. Combining eye-tracking and EFRP methods (64, 65) promises to advance the understanding of how disease-related changes in attention translate to failures in hazard detection while driving.

No difference was found between HM and HC groups in visual search performance. One possible explanation is that the stimulus display promoted highly efficient visual search performance. Visual search efficiency has been shown to be affected by target and distractor similarity (66). Displays comprising low target–distractor similarity (e.g., red target, black distractors) and high distractor–distractor similarity (e.g., all black distractors) promote efficient search, such that competing distractors fail to impose response time costs. Conversely, displays increasing in target–distractor similarity and decreasing in distractor–distractor similarity result in inefficient search, such that competing distractors impose response time costs that increase with distractor number. Thus, more complex visual search displays demand focused attention to discriminate between target and distractor search elements (67, 68). Here, the results indicate that performance is indistinguishable between cancer patients and healthy comparisons during efficient visual search. Future studies are needed to determine whether performance during visual search within complex displays is impaired in cancer patients.

EFRP measures can help probe how the brain processes information before, during, and after eye saccades. First, pre-saccadic shifts of attention enhance perceptual processing of

locations and features present in the saccadic targets (69, 70). Second, saccadic suppression inhibits neural activity in low-level visual regions during eye movements (71–73). Third, information processing is enhanced immediately following saccade offset (74, 75). Importantly, most of what we know about the neural mechanisms of visual attention during saccades has been gained through studies of non-human primates. EFRP studies in human subjects engaged in real-world relevant tasks may complement and advance our current understanding of visual attention mechanisms.

Limitations

First, this study is limited by a small sample size. Although study participation is ongoing for some patients ($n = 4$), these data will not provide sufficient power to overcome this limitation. Future large-scale studies will need to compensate for subject dropout for a variety of reasons, such as simulator discomfort (9%) and patient mobility restrictions (e.g., acute leukemia inpatients; 9%). Nevertheless, these pilot data provide promising initial evidence for reduced neural information processing in HM patients. Second, it is assumed that cancer biology and chemotherapy toxicity both contributed to reduced EFRP activity in HM patients. This study was designed to prospectively evaluate changes in performance during driving simulation, which included a pretreatment assessment for patients scheduled to undergo chemotherapy. Given the current number of HM patients who completed driving simulation, the authors are currently unable to dissociate contributions of cancer-related factors from chemotherapy-related factors. Third, EFRP activity while drivers completed the visual search task could not be reliably measured. EEG recorded during visual search included both stimulus-evoked activity and EFRP activity. It is not possible to dissociate these two patterns of activity with current methods. Thus, the study was unable to evaluate load-dependent changes in P1 amplitudes. Future studies will incorporate eye-tracking methods and non-visual attention tasks to reliably measure cognitive load-dependent changes in EFRP activity while driving.

Conclusion

Driving simulation, eye movement, and EEG measures were used to study visual attention and driving in cancer patients with HM. Lower EFRP activity following saccade offset was observed in drivers showing greater impairment in visual search performance while driving, consistent with previous studies showing EFRP activity is associated with task performance. Similarly reduced EFRP activity was found in drivers diagnosed with a HM; because of the high level of uncertainty estimated for this effect, further replication of reduced EFRP activity in HM drivers is necessary. In contrast, measures of saccade behavior such as frequency and magnitude were unrelated to both cognitive function and disease status. These results support a functional dissociation between saccade behavior and post-saccade information processing during driving and may serve as a neural measure of impaired information processing in diseased and cognitively impaired populations.

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Figure 1.

Driving Simulator and Visual Search Task. (a) Participants completed simulated driving scenarios in SENSEI (Simulator for Ergonomic, Neuroscience, Safety, Engineering, and Innovation). (b) Participants completed visual search tasks by responding with the direction of a red target stimulus presented among black distractors. Visual search displays were presented on the center display in SENSEI. During the driving (shown in b) condition, visual search stimuli were presented against the simulated background. During the baseline condition, stimuli were presented against a black background.

Figure 2.

EFRP results. (a, b) EFRP activity was measured by estimating mean EEG amplitude as a function of time relative to saccade offset (time = 0). PI activity (gray boxes) emerged approximately 100 milliseconds after saccade offset. (a) EFRP activity is plotted separately for healthy control (HC; blue line) drivers and drivers diagnosed with a hematological malignancy (HM; red line). (b) Drivers were split into two groups based on differences in visual search response time (RT) between driving and baseline conditions. EFRP activity is plotted separately for drivers showing smaller (low cost; black line) and larger (high cost; gray line) RT differences. (c, d) PI amplitude was estimated as mean EFRP activity during the PI time window (gray boxes in A, B). (c) PI amplitudes were larger for HC (blue) drivers compared with HM drivers (red; $p = 0.18$). (d) PI amplitudes were larger for drivers with low RT costs (black) compared with drivers with high RT costs (gray; $p = 0.03$).