Electrophysiological Results

- ERPs abnormalities have been linked as endophenotypes of cognitive deficits in neuropsychiatric diseases like schizophrenia, Alzheimer’s disease, PTSD, traumatic brain injury, and cocaine abuse.

- Mouse ERPs are analogous to human ERPs and can be used to study genetic and pharmacologic manipulations of complex human illnesses.

Discussion

- ERPs changes are potential markers of impaired brain function following chemotherapy.
- An animal model using ERPs could be used to screen future chemotherapy drugs and could help identify potential drugs to block these cognitive deficits.
- Our findings suggest that increased norepinephrine release and hyperarousal may play a role in the cognitive and behavioral changes associated with chemotherapy treatment.

References and Acknowledgements

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Figure 2

Cognitive Impairment Following Chemotherapy

- Long-term cognitive deficits are common complications after treatment of cancer with systemic chemotherapy, even for non-CNS tumors.
- Around one-third of cancer patients experience subtle post-chemotherapy cognitive decline (“chemo-brain”).
- Deficits are most apparent in:
  - Working memory
  - Executive functioning
  - Visuospatial abilities
  - Processing speed.
- Prevalence increased 3.5- to 8-fold with chemotherapy treatment.
- Can last as long as 10 years.

Methods

- Drug-treated animals showed significantly impaired gating one week after drug treatments were completed. There was no effect of drug on the amplitude of P1-N1 or latency of P1. The drug-treated animals also showed significantly increased freezing during fear conditioning and increased exploration without memory impairment during novel object recognition.

Conclusion: We conclude that chemotherapy causes decreased ability to gate incoming auditory stimuli, which may underlie associated cognitive impairments.

These gating deficits were associated with a hyporesponsive response to fear conditioning and reduced adaptation to novel objects, suggesting an additional component of emotional dysregulation. However, amplitudes and latencies of ERP components were unaffected, as was NOR performance, highlighting the subtle nature of these deficits.

Auditory Event-Related Potentials (ERPs)

- Electrodes are implanted in the hippocampus and referenced to frontal sinus.
- Electrical activity is recorded while animals are presented pairs of auditory clicks (S1 and S2).
- The signal is averaged to correspond with stimulus onset.
- ERP waveforms have reproducible, representative peaks that represent coordinated firing of generators in the auditory pathway, shown in Figure 2.
- Sensory gating represents habituation of neural responses to repetitive sensory stimuli (S1, S2). It can be measured as a ratio of peaks in S2 to those of S1.

ERPs Assess Sensory Processing

- ERPs are recorded at weeks 1, 3, and 5 after surgery.
- The last session occurred one week after drug treatments had finished. The components P1 (most positive peak between 10-30 ms) and N1 (most negative peak between 25-60 ms) were analyzed for amplitude and latency.
- Sensory gating was measured as the ratio of (P1-N1) for S1 to that of S2.
- Contextual Fear Conditioning (CFC): CFC was assessed 2 weeks after drug treatments were finished. During training, baseline freezing was recorded and then animals received two 1.5 mA scrambled footshocks. During testing, which occurred 1 and 14 days post training, animals were exposed to the conditioned context in the absence of shock and freezing response was recorded.
- Novel Object Recognition (NOR): NOR was assessed 1.5 weeks after drug was stopped. During training, mice were placed in the apparatus with two identical objects inside. During testing, animals were again placed in the apparatus but now one of the original objects was replaced for a novel one. Object exploration times and percentage preference were recorded during both phases.

Behavioral Results

- There was a main effect of drug on CFC (p = 0.045) with chemotherapy causing increased fearful freezing. There was a main effect of drug on total exploration time (p = 0.011) during NOR but not on novel object preference, with chemotherapy treated mice showing increased exploratory behavior.

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