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Assessing Neurocognitive Dysfunction in Cranial Radiotherapy: Can Cognitive Event-related Potentials Help?

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Cognitive changes are common sequelae of cancer and cancer treatment, particularly in patients receiving cranial radiotherapy (RT). These effects are typically assessed by subjective clinical examination or using objective neuropsychological tests. Biologically based neurophysiological methods have been increasingly applied to the study of cognitive processing in neuropsychiatric and neurological disorders and as objective measures of cognitive status for patients with dementia. These methods detect the activation of neural circuits that directly mediate cognitive function in the human brain and include metabolic and electrophysiology based techniques. Neuroimaging procedures such as 18FDG PET and more recently fMRI, which detect metabolic activation associated with cognitive processing, provide excellent spatial resolution and can be directly correlated with neuroradiological findings associated with cranial RT neurotoxicity. Clinical electrophysiology procedures such as cognitive event-related potentials (ERP), which detect the neuronal electrical activity associated with cognitive processing, offer excellent temporal resolution at low cost. Cognitive ERP techniques are already being used to assess severity and progression of cognitive dysfunction in patients with vascular and degenerative dementias, but have been largely overlooked in studies of radiation-related cognitive impairments. We review these various electrophysiological methods in the context of their relevance to assessing cranial RT effects on cognitive function, and provide recommendations for a neurophysiological approach to supplement current neuropsychological tests for RT cognitive impairments. This technology is well suited for clinical assessment of neurocognitive sequelae of cancer and should provide new insights into the mechanism of RT-related cognitive dysfunction.

Key words: Event related potentials; Psychometric testing; Evoked potentials; Radiation; Brain.

Introduction

Exposure of CNS tissue to ionizing radiation can trigger a number of toxic effects, many of which we have learned about through clinical experiences in treating cancer patients. In the context of radiotherapy (RT), the best understood and the most problematic of these effects is radiation necrosis, which has been recognized as a complication of cranial RT for over fifty years (1, 2). Necrotizing doses of radiation can produce debilitating cognitive sequelae. With conservative management, the incidence of radiation necrosis involving CNS tissue can be minimized, but this does not eliminate the risk of cognitive dysfunction. Mild to moderate cognitive deficits occur in the absence of tissue necrosis and affect a

Abbreviations: RT, Radiotherapy; ERP, Event related potential; CNS, Central nervous system; fMRI, Functional MRI; RTOG, Radiation Therapy Oncology Group; MMSE, Mini Mental State Exam; ALL, Acute Lymphocytic Leukemia.

significant number of patients undergoing cranial RT (3, 4). The overall incidence of cranial RT-related cognitive dysfunction in patients surviving more than six months has been estimated to be as high as 25% to 30% and is similar for patients receiving therapeutic and prophylactic cranial RT (5).

Cranial RT-related cognitive impairment typically presents as a delayed response, occurring from weeks to 24 months following treatment. General cognitive status (assessed by MMSE), memory, and attention deficits are most commonly reported. Early delayed effects have been shown to primarily involve verbal semantic associative memory processes (6). These early effects are reversible. Late-onset cognitive effects (appearing several months to many years post treatment) have been reported in various clinical studies; these effects involve a range of cognitive domains, including memory, language, intelligence, executive function, attention/vigilance, processing speed, abstraction, and perceptual processing, and can range from mildly to completely disabling (7, 8) (Table I). The cognitive profile for patients with dementia secondary to late radiation effects is indistinguishable from that observed in vascular dementia when patients are matched for general cognitive status using the MMSE (9). Similarities in clinical presentation to normal pressure hydrocephalus have also been noted. Deficits appearing even later (three to five years post treatment) have been observed in patients with low-grade primary CNS tumors involving visual memory (10).

Such deficits are not specific to cranial RT. Cognitive status is also a sensitive indicator of iatrogenic brain injury associated with the surgical and medical management of the cancer patient, and distinguishing the effects of RT from other treatment effects, the underlying disease, and concurrent illnesses can be problematic (3). Surgical procedures always carry a significant risk of postoperative cognitive dysfunction, particularly in the elderly. This has been extensively studied in the context of coronary artery graft surgery and other cardiac procedures involving cardiopulmonary bypass (11-13). But postoperative cognitive dysfunction is also observed in non-cardiac surgery and even in minor procedures (14). The adverse effects of chemotherapy on cognitive function have also been shown repeatedly in children and adults (15, 16), with the most severe manifestations occurring in association with leukoencephalopathy, a progressive and debilitating syndrome that can occur as either an acute or delayed response to chemotherapy (17, 18).

The number of published reports addressing the effects of cranial RT on cognitive status has steadily increased over the last thirty years since the first reports of cognitive dysfunction in children began to appear (Figure 1). Several considerations contribute to this interest. First and foremost, cognitive risk influences patient management. Cranial RT may be deferred or avoided because of the risk of cognitive dysfunction and its associated effect on quality of life (19-21), Second, new technologies for delivery of RT to the brain such as conformal proton therapy, stereotactic RT, stereotactic radiosurgery, and intensity modulated radiation therapy, may produce less cognitive dysfunction than conventional cranial RT (22-30). Third, cognitive status can be a sensitive indicator of disease progression and survival (31). Brown *et al*., reported that cognitive status prior to RT was a good predictor of 5-year survival in patients being treated for low-grade glioma; patients with moderate to severe cognitive

Table I
Continuum of cranial radiotherapy cognitive sequelae (and examples of neuropsychological measures to detect cognitive dysfunction)

Classification	Degree of functional impairment	Domains Affected	Evaluation
Sub-clinical to Mild Cognitive Impairment	Functional deficits with limited to no impact on daily functioning.	Deficits in at least one cognitive domain:	
		Memory	Digit Span; WMS-R
		Attention	Digit Repetition; Ruff 2 and 7 Tests)
		Executive function	Stroop Test, Wisconsin Card Sorting Test (WCST) ; Trailmaking Test-B
		Language	Controlled Oral Word Association Test; Token Test; Boston Naming Test
		Visual-spatial processing/ Visual motor sequencing	Rey-Osterrieth Complex Figure Test; Trail-Making Test
		Intelligence / Achievement	Intelligence / Achievment (WAIS-III, WAIS-R, WICS-R, WRAT-III)
Dementia	Functional deficits that produce impairment in occupational or social functioning.	Severe memory deficits plus one or more of the following:	MMSE
		Language: Aphasia Motor Planning: Apraxia Perceptual: Agnosia Executive Function: Frontal dementia	
Coma	Unresponsive or minimally responsive.	All cognitive domains affected	Coma Scales (e.g., Glasgow Coma Scale)

function exhibited significantly worse survival (progression free and total) (32). Fourth, as more aggressive approaches for managing patients with malignant primary CNS tumors extend survival times, the adverse effects of cranial RT, including cognitive dysfunction, become more likely. Kumar *et al*., reviewed a series of 148 patients with malignant gliomas enrolled in a research protocol consisting of accelerated RT with carboplatin (2 Gy per fraction, 3 fractions per day) followed by chemotherapy; they reported that a quarter of these patients developed radiation necrosis, with another third exhibiting neuroradiological findings of white matter damage (33). Although cognitive effects were not reported, other studies have shown a strong correlation between white matter damage and cognitive dysfunction (7). Fifth, procedures for assessing cranial RT related cognitive dysfunction are becoming more standardized. A recent clinical trial demonstrated the feasibility of applying a standardized battery of neuropsychometric tests in multicenter clinical trials (RTOG Protocol BR-0018) to the assessment of RT-related cognitive impairment (34). Finally, cognitive deficits are a good target for pharmacological management. As progress is made in developing neuroprotective and neurocognitive enhancing drugs for treating neurodegenerative and vascular dementia, new options will become available for preventing or reversing the cognitive deficits associated with cranial RT.

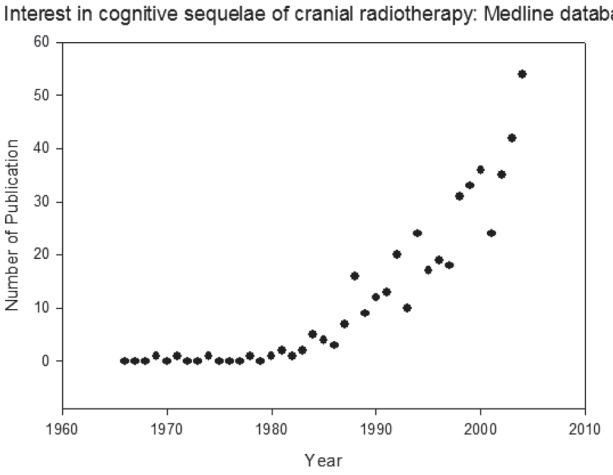

Figure 1: Cognitive sequelae of radiotherapy: Medline database search from 1966 to 2004. The first reports of cognitive dysfunction following cranial irradiation in survivors of childhood leukemia began to appear in the early 1980's. The number of publications assessing or addressing cognitive dysfunction related to radiotherapy has increased over the years, and has focused on both childhood and adult cancer patients.

A number of different approaches have been used to assess cranial RT-related cognitive dysfunction (Table II). Moderate to severe cognitive deficits are easily recognized with clinical observation. Formal assessment tools such as the MMSE offer a quantitative measure of general cognitive status, yet may not be sensitive enough to detect mild cognitive changes and are not designed to assess impairments in executive function (35, 36). Subjective, patient-reported assessments of mental function offer good sensitivity, but do not always correlate with more reliable objective measures of cognitive function. Neuropsychometric screening is the most common approach now used to assess RT-related cognitive dysfunction. Typically a battery of neuropsychological tests is given to identify abnormalities in specific cognitive domains. Neuropsychological tests offer sensitivity and objectivity, and the results are conceptually easy for patients and physicians to understand. However, formal neuropsychometric evaluation can be expensive and time-consuming. Moreover, these tests provide limited insight into the neurobiological basis underlying RT-related cognitive dysfunction.

Table II
Assessing Cognition / Higher Level Brain Function

Assessment	Type
Clinical Observations	Neurological Examination
	Mental State Examination
Neuropsychometric	Patient Reported
	Objective
Neurophysiologic	Metabolic based
	Event Related fMRI
	Electrophysiology based
	Event Related Potentials
	Reflex Based

Neurophysiological-based technologies make it possible to follow the neural activities mediating cognitive processes, behaviors, and even subjective experiences. Small-amplitude electrical and magnetic fields are detected from the scalp and associated with the generation of neural activity mediating higher-level functions. By synchronizing the acquisition of these electromagnetic signals to the presentation of a repeated cognitive stimulus, event-related potentials (ERP) associated with sequential stages of cognitive processing of the stimulus can be extracted from background noise.

We suggest that ERP may be applied to the investigation of cognitive impairment in patients undergoing radiotherapy, both as an objective measure of cognitive change caused by cranial RT and as a tool for identifying the neural basis of cranial RT-related cognitive dysfunction. We will review the use of cognitive ERP in related clinical domains, provide an overview of the components of the ERP, and propose a set of ERP-based screens for use in the clinical assessment of RT-related cognitive deficits.

Recording and Signal Processing of the ERP

ERP are derived from the electroencephalogram. Scalp electrodes are applied in specific locations according to the standard 10-20 system (37), either individually or using commercially prepared caps. With the individual electrode impedance at or below 5 kΩ, the signal is amplified using an

isolated differential amplifier, bandpass filtered between 1 and 40 Hz (the actual band will depend on the specific ERP component of focus), and digitized with a sample rate often around 250 samples per second. The sample rate is less for somatosensory or brainstem evoked potentials, given that the latencies are greater and the frequencies are lower for the targeted components. Segments of the electroencephalographic record, time-locked to the stimulus presentation extending for 1000 to 1400 ms beginning at least 100 ms before the stimulus, are screened for EEG artifacts (blinks, eye movements, other spurious EMG activity, slow voltage shifts), then averaged to derive the evoked potential (if the response is the time-locked event, a greater pre-event window is used). Typically, 20-30 stimulus repetitions are sufficient to compute a stable potential.

ERP are analyzed in the time domain. The baseline is computed as the mean potential for the 50 to 100 ms prior to stimulus onset and used to calculate the amplitude of the peaks and the associated latencies. Statistical decomposition methods such as principle component analysis can be used to provide more objective detection of time domain features (38). Such techniques have been used in preprocessing of ERP signal for source localization. If the ERP signal is simultaneously recorded through a high-density array of scalp electrodes, mathematical techniques have been developed that attempt to locate the origin of the surface potential.

Additional details on ERP methodology may be found in the Guidelines paper by Picton *et al*. (39-41).

ERP Paradigms

ERP techniques were developed as research tools by cognitive neuroscientists and have been used for over forty years to probe the neurobiological basis of cognitive processing. Although different acquisition paradigms have been described, they share a common conceptual base. Many cognitive tasks involve processing of auditory, verbal, and/or somatosensory information. In some cases this information is used in the selection of an appropriate response to a cue or question. For example, a patient is asked to respond to the higher of two tones. To complete this task, the afferent sensory stream generated by auditory receptors must be transmitted to the brain, relayed to sensory processing centers, a comparison of the current stimulus representation must be computed against a stored target representation, an appropriate response must selected, this selection communicated to motor processing centers that control the hands, and efferent signals sent to the muscles involved in the generation of a button-press response. Each step is implemented sequentially and in different regions of the brain.

The ERP records the spatial-temporal pattern of electrical activity generated by neural activity with the goal of distinguishing among exogenous and endogenous components of the cognitive processing sequence and comparing their modulation across stimulus and task demands (*e.g*., between the high and low tones). The ERP reflects the synchronized post-synaptic potentials generated by the depolarization of neurons, primarily the large pyramidal cells of the cerebral cortex. The endogenous responses involve the processing activities associated with the cognitive demands of the task. The exogenous components reflect the bottom-up, automatic response of the sensory analysis circuits to a stimulus, and are sensitive to the character and intensity of the sensory information.

In practice, acquisition of the ERP involves the presentation of a visual, auditory, or somatosensory target stimulus. The critical factor is that the onset of the presentation is time-locked with the EEG record. The target stimuli can be linguistic or non-linguistic, simple or complex (*e.g*., tones, colors, letters/numbers, objects, pictures, words, sentences, verbal, or printed). These stimuli may be associated with a cognitive task, in which case the subject is given instructions and/or training. But this is not essential; a passive paradigm may be used to assess perceptual processing. The type of stimuli and the context in which they are presented are flexible and make ERP adaptable to a wide range of cognitive processes. One of the most common ERP techniques is the oddball paradigm, in which two or more stimuli are presented but one stimulus occurs more frequently than the other. In the example above, the non-target low tone might occur 80% of the time. The target high tone, occurring on 20% of trials would be designated the oddball. Another variant is the oddball/habituation paradigm in which the subject is familiarized with one stimulus, and the responses to the presentation of familiar and novel stimuli are differentiated.

ERP Components

In the following paragraphs, we will describe a number of the commonly derived components of the event-related brain potential (summarized in Table III).

P50. The P50 is one of the earliest, centrally-generated ERP. It may be evoked by auditory, visual, or somatosensory stimulation and is generally considered to reflect activity in the primary sensory cortex. Thus, source localization places the auditory P50 generator on the superior temporal gyrus, probably including the primary auditory cortex and the planum temporale (42-44).

In addition to direct measurement of the P50 response to an individual stimulus, it is well known that the P50 may be used as an index of sensorimotor gating. Each of two sequential auditory 'clicks' that are presented with onset-to-onset latency of about 500 ms will evoke a P50. However, the P50 to the second stimulus of the pair is often signifi-

cantly reduced in amplitude in comparison to the first. This reduction or gating of the stimulus processing is often considered to reflect the ability of the perceptual structures to maintain focus without being rapidly distracted. Indeed, unlike individuals with ADHD who appear impulsive and lack the ability to sustain attentional focus, those with sensory gating deficits report objects and stimuli in the environment do not always organize into consistent groups; that is, there is an inability to attend to one object while inhibiting competing or background information.

N100. The N100 is generally regarded as the earliest component of the auditory ERP to consistently reflect endogenous modulation. In a standard auditory oddball task, subjects are asked to count the 'rare' tones presented to the left ear and ignore all tones in the right ear. Directing attention to one ear increases the magnitude of the N100 component to those stimuli in comparison to the stimuli in the unattended ear (45, 46). The divergence of the evoked potentials to attended and unattended stimuli represents the point at which measurable cognitive filtering of the stimulus input begins (41, 46). Source localization of the auditory N100 suggests that like the P50, its generators are located on the superior temporal gyrus near the primary auditory cortex (47, 48). Taken together with evidence that the source(s) of the visual evoked N100 may be localized to the extrastriate areas (*e.g.*, area 19), it is likely that the N100 reflects the activation of attended as compared with unattended representations by reentrant activation of early sensory association cortices (41, 49-51).

MMN. MMN is a negative-going ERP component that has a similar time course to the N100. It begins about 60 ms and peaks between 100 and 150 ms after stimulus onset. Like the N100, MMN is typically elicited using an auditory oddball paradigm. However, unlike the N100, MMN represents a difference wave, which is derived by calculating the difference between the ERP produced to oddball stimuli and that produced to the common stimulus. This difference gives rise to the name mismatch negativity. Unlike the oddball task producing the classic P300, the MMN is produced when subjects are engaged in passive listening or are focused on another task. Thus, the MMN is considered to reflect automatic, preattentive processing of deviant features or change detection (41, 52). The source of the MMN includes the superior temporal gyrus, which appears to be integral to the analysis and detection of change, and the frontal cortex, which in involved in the re-orientation of attention toward the change (53-55).

P300 (P3, P3b). The P300 has been the most common focus of ERP investigations, at least in part because it is clearly an endogenously generated component. When a subject's attention is actively focused on the stimuli in the oddball task, the oddball stimulus will elicit a positive potential with about 300 ms latency which is greatest over parietal scalp locations (also known as the P3 or P3b) (56). The stimuli may be presented in any modality, as long as the subject can discriminate among them (41, 56, 57). Importantly, the amplitude may be increased by making the task-relevant stimulus more infrequent (58, 59) or by increasing the processing resources necessary for successful performance of the task (60). In part, because the P300 seems to be sensitive to the difficulty or complexity of the task itself rather than to the mere difficulty of response selection, it is believed that the P300 is generated when the processing of a stimulus requires the updating of the repre-

Table III
Neurophysiological Measure.

Measure	Processes & Mechanisms	Anatomical Correlates/Source
Event-Related Potential		
P50	Exogenous. Stimulus activation of primary sensory cortex; P50 suppression is a measure of sensory-motor gating	Superior temporal gyrus including the planum temporale (for auditory stimluli)
N100	Endogenous. Orienting and attention to a stimulus	Superior temporal gyrus including the planum temproale (for auditory stimuli)
Mismatch negativity (MMN)	Exogenous. Automatic, preattentive processing of stimulus change / deviance	Superior temporal gyrus (for auditory stimuli)
P300	Process of updating working memory representation of current context, stimulus set, or environment	P3a: dorsolateral prefrontal cortex; supramarginal gyrus; cingulate cortex P3b: medial temporal cortex; superior temporal sulcus; superior parietal cortex; ventrolateral prefrontal cortex
N400	Language; semantic incongruity or novelty	Parahippocampal and fusiform gyri
Lateralized Readiness Potential (LRP)	Response selection, motor preparation	Pre-motor cortices
Error-Related Negativity (ERN)	Response monitoring; conflict monitoring	Dorsolateral prefrontal cortex; Anterior cingulate cortex
Reflex Modification		
Conditioning	Learning and association	Hippocampus; medial temporal lobe; cerebellum
Prepulse Inhibition	Sensory-motor gating	Septohippocampal pathway; Striato-pallido-pedunculopontine pathway
Emotion-Modulation	Processing of the emotional and motivational context	Orbitofrontal cortex; ventromedial frontal cortex; anterior cingulate; amygdala

sentations of the stimulus environment or context currently held in working memory (41, 59, 61-64). The P3b appears to involve frontal areas, including the ventrolateral prefrontal cortex (65-67), temperoparietal cortices, including the intraparietal sulcus and superior parietal cortex, superior temporal sulcus, and medial temporal areas, including the hippocampal, parahippocampal, and entorhinal cortices (65, 68-72).

P3a. In addition to the classic P300 (or P3b), a positive component with a similar latency but a maximum over frontal scalp locations may be observed when an unexpected or novel stimulus is inserted into the stream of stimuli of the oddball task (73). This novelty-related P300 (or P3a) can be produced to the first occurrence of any new stimulus, such as the oddball stimulus during the first block of practice trials; however, as memory representations for the stimuli are constructed, the topography shifts to the parietal maximum (74). The P3a appears to involve activation of the anterior cingulate and dorsolateral prefrontal cortices in their role in working memory as well as the supramarginal gyrus (65, 75, 76).

N400. The N400 is a partially distributed language-related component. It was first recorded to the presentation of semantically incongruous words (*e.g.*, the pizza was too hot to "eat/cry") (77-79) and has since been observed in many contexts in which a word or picture is unexpected or incongruous with the preceding semantic context. For example, it appears in picture-verification paradigms in which subjects indicate if a picture matches the category of previously presented word, and sentence-verification paradigms in which subjects indicate whether or not a sentence is true. In the latter, N400s are generated both by false but incongruous sentences ("a bird is a tree") and by incongruous sentences ("a bird is not a tree"). The N400 appears to be generated bilaterally in the parahippocampal anterior fusiform gyrus (80, 81).

CNV. The contingent negative variation (CNV) is a slow potential that develops over frontal and central scalp locations and reflects stimulus expectancy or the anticipation of an event. It is computed by averaging relative to the second stimulus in a S1-S2 paradigm. In this paradigm, the first stimulus serves as a warning to prepare for the presentation of the second stimulus that is presented after a fixed interval and requiring a motor or cognitive response. The CNV begins to develop after the warning stimulus and reaches its most negative at the presentation of the imperative stimulus.

LRP and ERN. Two evoked potentials that are time-locked to the subject's response rather than a stimulus presentation are the lateralized readiness potential (LRP) and error-related negativity (ERN). The LRP is derived by comparing the potentials recorded over each motor cortex. Activity in the contralateral motor cortex may be observed prior to execution of a response. In paradigms with two possible responses (*e.g.*, one button press for each hand), conflict in the decision process may be observed as activation of the LRP for the incorrect response prior to execution of the actual correct response (41, 82). The ERN is recorded at central scalp locations and is likely generated by frontal circuits including the anterior cingulate cortex (83-85). It is generated when subjects perform an erroneous response and are aware of the fact. It appears as an increased negativity between 50 and 150 ms following the execution of the error.

Related Electrophysiological Techniques

Sensory ERP. Sensory ERP are triggered by the afferent impulses from tactile, auditory, or visual sensory stimuli passing through brain sensory relays onto cortical and subcortical processing centers. Somatosensory ERP provides a measure of the transmission time between locations in sensory pathways from the upper and lower limbs. The brainstem auditory evoked potential provides analogous information from the auditory system. In each, a series of stimulations and the resulting potentials are recorded, and the resulting averaged waveform is then scored for the latencies of the series of peaks. Changes in latency to or between specific peaks are interpreted as deficits in transmission at specific nuclei. The amplitudes of the peaks may also be informative. A decrease in amplitude, or flattening of the peak, may indicate a decrease in the magnitude of the synaptic activity at a given nucleus. Spinal motor reflexes, such as the myotatic reflex or the Babinski reflex, are examined for changes in amplitude or timing. Parallel in conception, but less technologically intensive (or precise), increases or decreases in reflex amplitudes provide information regarding the competence of descending motor pathways and the segmental reflex circuitry.

Startle Response. The startle response is a defensive reflex organized in the brainstem; it consists of a characteristic pattern of muscle contractions (86). It is sensitive to multiple sensory modalities and may be elicited by a sudden onset of noise, light, or cutaneous stimulation (87-89). The nucleus reticularis pontis caudalis (NRPC) is the organizational locus of the final common output for the response (91, 92).

In humans, the startle eyeblink is measured by applying surface recording electrodes to the skin immediately below one eye to record the activity of the muscle, *orbicularis oculi*. The EMG signal is amplified, bandpass filtered (*e.g.*, 1-250 Hz), rectified, and recorded at 500 to 1000 samples per second [for details, see the "Guidelines" paper by Blumenthal and colleagues (93)]. This EMG record may be scored on a trial-by-trial basis for EMG response amplitude and onset latency within a window of 20 to 120 ms after stimulus onset.

Finally, a non-startling stimulus that precedes a startle-eliciting stimulus with an inter-stimulus interval of about 30 to 250 ms produces a profound inhibition of the startle response. This prepulse inhibition phenomenon is a measure of sensorimotor gating but has been demonstrated to be a significantly independent measure from the P50 (94, 95). Prepulse inhibition appears to involve forebrain circuits including the hippocampus, basal ganglia, and pedunculopontine tegmental nucleus (96) and has been used as a behavioral probe for modulations of dopamine and glutamate system activity, particularly in the context of schizophrenia (97, 98).

ERP: Relevance to RT Cognitive Dysfunction

The P50 is generally considered to be normal in individuals with Alzheimer's disease (AD) and subcortical dementias such as Huntington's disease (99-101). However, there are reports that patients with mild cognitive impairment and in the early stage of suspected AD produce P50 amplitudes that are increased in comparison to healthy, age-matched controls (102-104) as well as in age-matched 1st-degree relatives of AD-diagnosed patients (105). This P50 facilitation in mild or early dementia may represent an early indication of risk because it was observed in individuals where there was no change in the response time performance of the associated task (102).

Individuals with schizophrenia fail to show the P50 supression phenomenon (106, 107). Patients with AD display a similar gating disruption (99). Moreover, the reduction of P50 suppression has been employed as an index of increasing traumatic brain injury severity, in which it appears to be related to a reduction in tone in basal forebrain and mesencephalic cholinergic nuclei (108).

P50 appears as a likely candidate ERP to be sensitive to radiologically-induced damage in CNS function. As an early potential, its control is primarily exogenous, similar to the early and mid-latency components of the somatosensory evoked potential. Nevertheless, it may be sensitive to changes in tonic descending influence on the auditory cortex as observed in the P50 facilitation of early AD as well as the automatic stimulus analysis producing sensory gating. If the effects of RT appear as dementia-like processes, these might be reflected in the earliest stage, as a facilitation of P50 amplitude and subsequently as a reduction in P50 suppression.

There have been a number of studies in which the N100 was recorded while subjects with AD performed an auditory oddball task. The most frequent report has been that the N100 is not significantly different in demented and age-matched control groups (101, 102, 105). However, the N100 was observed to be smaller and to peak later in patients with Parkinson's disease, vascular dementia, and multiple sclerosis compared to controls (109-111). Demyelination is characteristic of the latter conditions and suggests the N100 may also be sensitive to RT-induced white matter damage. Parageogiou *et al*. (112), observed no immediate effects of prophylactic whole-brain exposure on N100. However, for patients with hippocampal and temporal lobe targets, late-appearing effects associated with white-matter changes would be expected to appear as changes in the N100.

In contrast to N100, the MMN is typically reduced in amplitude and delayed in AD (and likely Parkinson's disease as well) (113-115). The association of dementia with impaired MMN, along with the lack of a requirement that conscious attention be focussed on the eliciting stimulus set, suggest that MMN should be useful in the assessing processing deficits in patients with RT related dementia.

Because the P300 is generated during working memory and attentional processing, its use with clinical populations has been largely as an index of delayed processing and cognitive impairment. Although there have been occasional negative results (116-119), nearly three decades of work reveals a predominance of evidence that P300 latencies are prolonged (and may be of smaller amplitude as well) in patients with dementia (101, 120-122). Much of this work has involved patients with AD, in whom, beginning in the earliest studies (123), investigators have observed longer latencies for P300 in comparison to age-matched control groups (124-133). The latency effect has been observed with both auditory- and visual-evoked P300 potentials (101, 134-136). Furthermore, the P300 latency delay also appears in patients with subcortical dementias such as Parkinson's (111, 137-143) and Huntington's disease (135, 144, 145). Importantly for the consideration of RT-induced effects, the P300 delay has also been observed in patient populations with demyelinating conditions such as vascular dementia (110, 139, 146-148) and multiple sclerosis (109, 149-151).

Other characteristics of the P300 suggest its utility in the assessment of radiation-induced cognitive impairment. A number of studies have indicated that P300 latency changes are statistically associated with decreased performance on neuropsychological assessments, including the Stroop Test, the Wisconsin Card Sort Test, as well as general intelligence and concentration (132, 152-154). Additionally, while the changes in the P300 may correlate with changes in screening tasks such as the MMSE (136, 140, 154), an increase in P300 latency or decrease in its amplitude may be observed prior to diagnostically determinative neuropsychological indices and without changes in MMSE scores (137, 150, 155-159).

This characteristic of sensitivity to impairment of executive function, taken together with the possibility of assessing the progression of cognitive status more effectively than with

screening tools such as the MMSE, suggest that the P300 potential would be particularly useful in longitudinal assessment of patients receiving RT or radiosurgery for targets requiring CNS exposures (101, 121, 160). Such longitudinal investigations have described the progression of Alzheimer's dementia (121, 161), and have distinguished it from patients with Korsakoff's syndrome (162).

The involvement of dorsolateral prefrontal cortex, the anterior cingulate, and the hippocampal formation in generation of the P300 suggest that this component may be related to memory. Indeed, in implicit learning paradigms, the P300 amplitude recorded during the learning phase predicts subsequent memory performance (163-168). These data suggest that the P300 might provide additional information regarding brain function on tasks such as verbal and visual memory, which have previously been reported as sensitive to radiation-induced cognitive impairment.

If the language comprehension circuits are intact, it may be expected that the N400 will be normally produced in response to incongruous or semantically unexpected stimuli. However, if language-related areas are damaged or the distributed processing areas are disconnected by white matter damage, it may be expected that the N400 will be abnormal. Thus, for example, in patients with AD, the N400 has often been reported to be smaller and/or prolonged in comparison to age-matched control subjects (169-173). Subcortical white matter abnormalities are routinely observed in patients as a delayed response to RT along with impairments in language function, and the N400 would offer an objective measure to follow the progression of functionally significant subcortical damage particularly in parahippocampal anterior fusiform gyrus.

As an index of the ability to anticipate an event, the CNV has been demonstrated to be smaller and/or not well timed relative to S2 in clinical populations with frontal cortex damage. Patients with epilepsy and frontally-focused complex partial seizures (174), vascular dementia (175), or stroke (176), as well as patients with Parkinson's disease (137) or early AD (177-179) have all been reported to show decreased amplitude and/or increased latency of the slow wave CNV in a standard paradigm requiring a speeded button press to an imperative stimulus.

The ERN appears to be sensitive both to the level of conflict requiring resolution in the task and to the degree to which the subject is motivated to perform accurately (180-184). Neither the LRP nor the ERN has been used extensively in populations with cognitive impairment. However, in one series of studies examining the LRP in patients with AD, it appears that the patients were less able to suppress the development of the conflicting erroneous response in comparison to age-matched controls (185, 186). Similarly, in two studies reporting the ERN in patients with AD, error detection and monitoring appeared to be intact (the ERN appeared on error as compared with trials) but was diminished in comparison to age-matched control subjects (smaller and delayed ERN) (187, 188).

In many of the earliest investigations, the startle eyeblink was employed as an unconditional response to investigate learning and conditioning (193, 194). This approach allowed the principles of behavioral conditioning to be tested in humans as well as laboratory animals. Subsequently, the startle response has been used as a probe to examine the momentary state of the nervous system (at least that of the NRPC) under various contexts. One series of studies examined the effect of directing attention toward or away from stimuli, searching for behavioral evidence of attentional modulation. In these studies, attending toward the sensory modality in which the startle-eliciting stimulus was delivered potentiated the response and attending toward another modality inhibited it (88, 195-198). These data indicated that the focus of attention could modulate the transmission of modality-specific signals early in perceptual processing.

More recently, the startle probe approach has been applied to the study of emotion. One approach, the fear potentiated startle technique, is descended from the conditioning literature. In this paradigm, a stimulus, such as a light is paired with an aversive event such as an electric shock during the training trials (91, 199). When tested, the startle response is found to be potentiated if elicited in the presence of the light as compared to elicitations in the dark. This effect is produced by projections from the central nucleus of the amygdala to the brainstem startle circuit, including the NRPC (200-202). This approach has been useful in the investigation of neural substrates of fear and anxiety, for example, drugs which act as anxiolytics will reduce the potentiation of the startle response to the light without inhibiting the baseline magnitude of the response (91, 203).

A complementary approach assumes that in the presence of an emotional stimulus, reflexes congruent with that stimulus will be facilitated while those incongruent will be inhibited (204-207). Thus, the startle response as a defensive reflex will be facilitated in a negatively valent and inhibited in a positively valent emotional context. A common technique for this approach asks subjects to view a series of emotionally evocative images from the International Affective Picture System (208), while receiving occasional startle probes. Startle responses elicited in the presence of negative pictures are facilitated compared to those elicited in the presence of positive pictures (206, 209). This technique has provided a robust paradigm for investigations requiring the manipulation of emotional context.

Much of the work examining blink reflexes in patients with or at risk for cognitive impairment has used the blink reflex

elicited by electrical stimulation of the supraorbital nerve or the glabella-tap response. These data demonstrate that the blink reflex is delayed and has diminished habituation in both Parkinson's disease (189) and Huntington's disease (210-213). Additional research has indicated that the increased blink reflex latency in Huntington's disease is associated with the severity of motor symptoms (214, 215) and appears in asymptomatic individuals carrying the gene (216).

More recently, there have been applications of blink reflex conditioning, prepulse inhibition, and emotion modulation paradigms to assess changes in higher-order and distributed processing mechanisms for clinical populations. Patients with AD require significantly more training to successfully acquire eyeblink conditioning, a result which is linked to the decrease in cholinergic transmission in the hippocampus (217-220). Moreover, the magnitude of prepulse inhibition has been reported to be reduced in patients with Huntington's disease (221-223) as well as those with Parkinson's disease (223-225), but not in AD (225, 226). These data suggest that in these human clinical populations, prepulse inhibition may be more sensitive to degeneration of the striato-pallido-tegmental than hippocampal circuits. Finally, there have been two studies using the emotion modulation paradigm in patients with CNS damage. In one, a patient with blindsight resulting from stroke remained sensitive to the emotional valence of pictures as demonstrated in the modulation of the startle response (227). In the other, patients with traumatic brain injuries involving the frontal lobes failed to exhibit the modulation of the startle response produced by non-injured controls (228). Taken together, these studies suggest the utility of startle reflex modification paradigms for investigating the functional integrity of striato-pallido-tegmental (using prepulse inhibition), hippocampal and medial temporal cortex (using conditioning), and fronto-limbic (using emotional modulation) circuits in RT patients.

ERP Applied to Cranial RT-related Cognitive Assessment

Several studies have shown the utility of ERP for the assessment of cognitive impairments in patients following cranial RT. The first applications of ERP to the study of RT-related cognitive dysfunction appeared over 15 years ago. Moore *et al*., recorded auditory ERP in a population of 33 long-term survivors of childhood cancer (229). An auditory oddball paradigm was used, and both early and late potentials from the ERP recordings were analyzed for latency and amplitude. A strong correlation was observed between P300 latency and the presence of visuospatial deficits and a weaker but still significant correlation with IQ in this patient population. All patients were asymptomatic at the time of testing, and all were at least five years in remission.

Sato *et al*., (230) were able to distinguish a significant prolongation in P300 latency (auditory oddball paradigm) in children with acute lymphocytic leukemia (ALL) treated with CNS radiation in combination with intrathecal and intravenous methotrexate in comparison to age-matched controls. In contrast, children treated with chemotherapy alone tended to exhibit a shortening of P300 latency. The children who developed neurologic symptoms (convulsion, gait disturbances) during or after treatment demonstrated prolongation of P300 latency. Heukrodt *et al*., (231) reported similar findings in long-term ALL survivors, as well as in patients treated for solid tumors outside the CNS who received no cranial RT. Muchi *et al*., (232) failed to detect an effect of P300 latency associated with cranial irradiation in children two years after ALL treatment, although a P300 delay was observed in children who had presented with initial CNS involvement.

Uberall *et al*., (233) observed P300 abnormalities in long-term, disease-free survivors of childhood ALL. Using a visual oddball paradigm (checkboard reversal stimuli), ERP were recorded and the effects of treatment and disease on P300 latency and cortical distribution were assessed. Patients receiving prophylactic cranial RT in combination with chemotherapy showed significant prolongation of P300 latency as compared to patients treated with chemotherapy alone. No difference in P300 latency was observed between chemotherapy patients and a group of age- and gender-matched healthy controls. Significant differences in the spatial distribution of the P300 potential were observed in both treatment groups as compared to healthy controls. P300 latency was found to correlate with neuropsychological measures of non-verbal memory function, attention, and intelligence. Correlations were also made between cognitive status and P300 cortical distribution. P300 amplitude was abnormally high over the parietal-temporal regions of the right hemisphere in both treatment groups, and associated with visual memory deficits. Lower amplitudes were observed in the radiation treated group over the left frontal regions associated with concentration ability.

To the best of our knowledge, only one attempt has been made to use ERP for assessing adult cancer patients. Parageorgiou *et al*. (112), recorded auditory ERP in a short-term memory paradigm in eleven patients with small-cell lung cancer one month following prophylactic whole-brain RT. Exogenous and endogenous ERP components were analyzed, and the post-treatment latencies and amplitudes were compared to baseline values. Although no changes from a pre-irradiation baseline were observed in any of the analyzed ERP components (P50, N100, P300, N400), neither were significant changes observed in the digit span Wechsler test, the only neuropsychological cognitive measure examined in this patient group.

Most recently, an auditory stimulus-based oddball paradigm was used to evoke ERP in 10-year survivors of childhood cancer (234). In addition to measuring P300 latency, which was, as in prior studies, found to be significantly different

in cancer survivors as compared to age-matched controls, a mismatched (MMN) P3a component was analyzed, but was not found to differ in the long-term cancer survivors and age-matched, healthy controls. No neuropsychological measures were reported. The auditory stimulus used in this study involved simple tones, and it is possible that a more complex auditory stimulus, one more sensitive than tones, would have been more appropriate for the assessment.

Suggestions for Neurophysiological Assessment Strategies

We believe that cognitive ERP components, supplemented by reflex modulation techniques, may be useful in the assessment of patients following cranial RT. It is clear that a number of the ERP components are sensitive to the processes of dementing pathologies, including AD, subcortical dementias, and vascular dementias, as well as to trauma and stroke-induced damage. Moreover, it is this sensitivity, taken together with the relative ease and cost-effectiveness of the protocols that suggest the practical utility of the integration of neurophysiological assessment into the program of care for patients receiving cranial RT.

One approach is to tailor the selection of measures based on a risk assessment for each patient. Each assessment would include passive and active versions of the oddball paradigm examining the P3b component of P300 (as described above) for latency shifts, and the assessment of attention and basic executive function using, for example, Digit Span, Digit/Symbol Coding, the Stroop Task, the Trail Making Test, and a version of the Continuous Performance or the n-Back Task. In addition, based on the examination of the relative radiation exposure of various brain structures for an indication of the most likely areas of demyelination and necrosis, specific additional tasks could be included. For example, if the primary RT target is in the medial temporal lobe, a memory task for both verbal and visual memory using the P300 would be included. A series of words or geometric line drawings could be presented during a study phase followed by a recognition test using both the studied and novel items. An increased latency or a failure to observe increased amplitude in the P300 for subsequently remembered items may be indicative of a functional deficit. If the posterior language zones, including the planum temporale, surpramarginal gyrus, angular gyrus, or Wernicke's area, received significant exposure, the patient's assessment might include neuropsychological assessment of language examining naming (*e.g.*, Boston Naming Test), reading (*e.g.*, National Adult Reading Test), and writing (spontaneous writing, writing to dictation, and copying) as well as examination of the N400 response to semantic incongruities. In sentences presented one word at a time, impaired linguistic processing would be indicated by an amplitude reduction or latency increase of the P400 to unexpected as compared with expected final words (*e.g.*, The garden contained many rows of sofas/flowers). Finally, an assessment tailored for anterior exposures might supplement neuropsychological data from tests of verbal fluency (*e.g.*, FAS verbal fluency, category naming, Controlled Oral Word Association) and the tests of executive function, attention, and the standard P300 oddball task with an assessment of the P3a component of the P300 response, the contingent negative variation using a warned reaction time task, as well as assessment of the ERN using a standard flanker task (181, 183) and emotion modulation of the startle response (207-209). Decreased P3, CNV, or ERN amplitudes, or variations in peak latency would be indicative of impaired processing in frontal circuits. Similarly, the lack of a valence modulation, despite appropriate valence ratings, might be indicative of impairment in the evaluation or processing of motivational information.

An alternative approach to the integration of information from cognitive ERP into the care and follow-up of patients receiving cranial RT would involve implementation of a standard assessment protocol. An example protocol might begin with the presentation of a series of words (or pictures) for a subsequent memory test. The patient could then be given a task for attentional focus, such as viewing a silent movie. During this second phase a sequence of noise clicks could be presented to assess P50 and P50 suppression, followed by a series of high and low tones presented with an 80:20 probability to probe the passive response to an oddball. The third phase of the assessment would involve instructed, active tasks. First the oddball sequence would be repeated with the instruction for the patient to respond each time the target (rare) stimulus was presented. The N400 could be assessed using a picture verification task in which one of two buttons is pressed when the picture matches the category of a presented word, and the other button is pressed when the picture mismatches the category. To complete the third phase, a choice reaction time task could be used to examine the CNV (as well as the LRP). In the fourth phase, a series of words (or pictures) would be presented to assess recognition memory for the items presented in the first phase. In a final phase, prepulse inhibition and emotion modulation of the startle response would be measured. Data collection for this protocol could be completed in less than 60 minutes, with the entire assessment lasting approximately 90 minutes. The data from a standardized cognitive neurophysiological battery such as this would be combined with a standard neuropsychological battery (*e.g.*, the Halstead Reitan Battery of the Neuropsychological Assessment Battery) to provide a comprehensive outcome monitoring. Use of the full battery would document the progression of patient competencies as well as impairments following RT.

Currently, a limitation to the use of these neurophysiological approaches is that there are no normative values to allow for

independent evaluation of an individual patient. This situation can be ameliorated by the consistent application of a standard assessment battery to collect those data. However, even without normative data, ERP and reflex modification data are well suited to tracking the progression of an individual patient's condition across successive examinations. Optimally, comparison data should be collected prior to cranial RT and then evaluated against subsequent assessments at 6-month intervals. It is likely that these data will be most useful in the evaluation of patients with minimal apparent deterioration. The pattern of latencies/amplitudes of individual ERP components and reflex measures may provide a more complete description of the functional state of the various cognitive processes and assist in interpreting results for standard neuropsychological assessments. In addition, changes observed from one assessment to the next may indicate prodromal effects and could potentially be used to identify patients at risk of significant future decline.

Conclusions

Cranial RT remains a standard of care for many cancers, but carries with it a risk to the patient for cognitive impairment. White matter disturbances secondary to demyelination and vasculature injury are generally accepted to play a role in RT cognitive dysfunction, and neurophysiological techniques are particularly well suited to detecting subtle disruptions in white matter function. Although not widely used, ERP components have been shown to correlate with neuropsychological measures of RT-sensitive cognitive functions, including non-verbal memory, attention, processing speed, visuospatial processing, and intelligence. Formal neuropsychological assessment can help identify patients experiencing RT-related cognitive disturbances. Electrophysiological-based techniques offer a means of defining the neurobiological basis for these impairments, and perhaps provide the rationale for developing effective interventions to reverse or alleviate these cognitive sequelae. This technology is deeply rooted in the cognitive neurosciences, and the translation of these techniques to the clinic creates a link to an extensive body of knowledge on the neural basis of cognition. ERP and startle responses provide a functional approach to localizing the neural circuits contributing to cognitive deficits that complement neuroimaging studies and neuropsychological approaches.

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