CHANGES OF EVENT-RELATED POTENTIALS AS MARKERS OF EARLY BRAIN DAMAGE FOLLOWING IONIZING RADIATION. STATE OF THE ART AND FUTURE PERSPECTIVES

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Abstract

Several and converging findings indicate that, besides the increased cancer risk, ionizing radiation (IR) exposure may favour the development of abnormal vascular and degenerative processes that may cooperate to induce central nervous system (CNS) damages. Indeed, the brain is one of the most sensitive organs to the detrimental effects of even low and intermediate IR doses. This represents a critical issue involving especially categories exposed to IR, such as workers of nuclear plants, or interventional medical and nurse staff.

Therefore, it seems crucial to promptly recognize early signs of IR-induced brain abnormalities, in order to prevent and/or treat them appropriately

The recording of event-related potentials (ERPs) is one of the most common neurophysiological methodologies to record and assess evoked brain activity. ERPs have been used for decades to assess perception, cognition, and emotions even in neuropsychiatric disorders, as well as in neuroscience and psychology.

The aim of the present paper was to review the available literature data on the possible use of ERPs as possible marker of brain damage following IR exposure.

Although further studies are needed, nevertheless the careful literature review seems to suggest the potentiality of ERPs recording as an easy and bloodless mean to detect early brain abnormalities following IR exposure.

Key words: ionizing radiation, brain, event-related potentials, components of event-related potentials, Chernobyl disaster

Declaration of interest: none

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Introduction

It is undisputable that, besides the increased risk for cancer, ionizing radiation (IR) exposure may lead to additional ill-defined effects including atherosclerotic, cardiovascular, cerebro-vascular and neurodegenerative alterations (Marazziti et al. 2012). Indeed, the central nervous system (CNS) appears particularly sensitive to the detrimental action even of low and intermediate IR doses (Loganovsky 2002, 2009; Loganovsky and Yuryev 2001, 2004; Lowe et al. 2009; Alatas 2015; Betlazar et al. 2016). The ensuing negative effects are supposed to be the results of the interplay between vascular and cellular damages. Molecular studies of brain irradiation in animals and humans provide evidence of different abnormalities, such as apoptosis, neuro-inflammation, loss of oligo-dendrocyte precursors and myelin sheaths, and irreversible damage of the neural stem compartments with long-term impairment of adult neurogenesis (Wong & Van der Kogel 2004; Loganovsky 2009; Marazziti et al. 2012, 2014; Kempf et al. 2013; Katsura et al. 2015; Suresh Kumar et al. 2015; Seibert et al. 2017). Interestingly, the cortico-limbic system seems the primary target of brain IR damage with consequent dysfunction of hippocampal neurogenesis (Loganovsky 2009, Caceres et al. 2010, Allen et al. 2013, Acharya et al. 2015).

Recently, we detected time-related abnormalities in the left hemisphere of a group of interventional cardiology staff (Marazziti et al. 2015), and other authors in neurosurgeons exposed to IR (Zaidi et al. 2016). Therefore, it seems important the prompt and early detection of IR-related brain dysfunctions before they become irreversible, possibly through easily accessible and bloodless means. This is crucial in certain workers' categories exposed to IR, such as interventional medical and nurse staff, or personnel of nuclear plants, as well as in the crews involved in space exploration.

The recording of event-related potentials (ERPs) is one of the most common neurophysiological methods to assess evoked brain activity. An ERP is defined as any stereotyped cerebral electrophysiological reaction to a stimulus and, in particular, as "the measured response of the brain that is the direct result of specific sensory, motor or cognitive events" (Luck 2005). ERPs are measured by an electroencephalography (EEG) monitoring (Luck 2012a, b), and they have been used

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for decades to assess perception, cognition, motor events and emotions even in neuropsychiatry, cognitive psychology and neuroscience, and to investigate brain development during lifetime.

The aim of the present paper was to review the currently available literature data on the possible use of ERPs as possible marker of brain damage following IR exposure.

Methods

The systematic review was carried out according to the PRISMA guidelines (Moher et al. 2009) through searching PubMed and Google Scholar for English language papers from January 1990 to January 31, 2018. The keywords used and combined with "Event-related Potentials" were "Ionizing Radiation" "Brain" or "Brain Damage" or "Humans" or "Exposed Workers".

Articles were searched by all authors: they agreed not to include conference abstracts or posters, while case reports were considered if published in indexed journal. The following inclusion criteria were adopted: studies carried out in clinical sample of children/adolescents and/or adult; reliable ERP assessment through standardized methods, and use of reliable laboratory tests for biological measures. A total of 103 papers were included in the review, five were reviews and the remaining 98 were research papers.

Event-related potential: definition and characteristics

Pauline and Hallowell Davis (USA) were the first scientists to register acoustic ERPs (Davis, 1939). In 1964, the first cognitive component of ERP, defined as "contingent negative variation" (CNV), was described (Walter et al. 1964). The next year, Sutton, Braren, and Zubin (1965) discovered the P3 component. Over the next decades, ERP component research became popular. The introduction of computers in the eighties opened up new perspectives in the application of ERPs in cognitive neuroscience research. Since then, the use of ERP to investigate brain functions has increased constantly. Further, currently, ERP registration remains one of the most advanced techniques to investigate the physiology of sensory, cognitive and motor events associated to the information processing, and it is also considered comparable with functional magnetic resonance imaging (fMRI) (Luck 2012a, b; Handy 2005), while being cheaper .

ERP is the brain response that can be measured as the direct consequence of a sensory, motor, cognitive or emotional event. The ERPs triggered by sensory stimuli are called sensory-related potentials (SEPs), and they are further distinguished in: visual, auditory, brainstem auditory, and somatosensory. It is noteworthy that some terminology contradictions might be present in the literature, as an ERP is considered a synonym of evoked potential (EP) (Luck 2012a, b). At the same time, ERP is regarded as a synonym of EP to endogenous (cognitive) events relating to expectations, recognition, decision making and initiating motor response. Thereby, a distinction is made between sensory EP and cognitive EP or ERP (Shagass 1972, 1975; Gnezdickij 2003; Zenkov 2011).

ERPs consist of several components reflecting specific neurocognitive processes (Luck 2012a, b). ERP waveforms are composed by a positive and negative voltage deflections related to a set of different components (Luck 2005). Although some ERP components are referred to with acronyms (e.g., contingent negative variation, CNV), the majority of them are indicated by a letter (N/P) indicating the polarity (negative/positive), followed by a number indicating either the latency in milliseconds or the component's ordinal position in the waveform. A negative-going peak, that is the first in the waveform and often occurs about 100 milliseconds after a stimulus, is often called the N100 (indicating that its latency is 100 ms after the stimulus and that it is negative), or N1 (indicating that it is the first peak and is negative); it is often followed by a positive peak, usually called the P200 or P2. The stated latencies for ERP components are often quite variable, particularly those of the later components which are related to the cognitive processing of the stimulus. For example, the P300 component may exhibit a peak anywhere between 250 and 700 ms. This component has been related to the process of decision-making, and it is assumed to be the result of an endogenous potential, while reflecting the processes related to the stimulus assessment or categorization. P300 during EEG recording is recorded as a positive voltage deflection with the latency period (delay between stimulus and response) of 250-500 ms (Polich 2007, van Dinteren et al. 2014). Schizophrenia is an example of the possible use of ERP in psychiatry. Indeed in this condition, suppression of the P50 component of ERP response to repeated identical auditory stimuli has been widely reported (Sakkalis 2015). Again, schizophrenic patients tend to have a reduced P300 in several brain regions, but particularly in the left temporal lobe (Salisbury et al. 1998). Notably, a smaller P300 response over the left superior temporal gyrus seems to predict more severe positive and negative symptoms (Kawasaki et al. 2007)

Effects of IR on ERP

The first study reporting changes of induced brain electrical activity after IR exposure was carried out in Japan (Minamizawa et al. 1967), however, subsequent data did not confirm previous findings (Minamizawa and Tsuchiya 1977, Minamizawa et al. 1980). Other authors described a remote brain dysfunction, primarily in the left hemisphere, by means of vestibular EP, following low doses of x-rays (Yaar et al. 1979, 1980).

After the Chernobyl disaster, the interest in EP alterations induced by IR increased significantly and involved specifically some of the authors of this paper (KL and KK). It was reported that even a single X-ray pulse (pulse dose - $1{,}7 \times 10^3$ $Gy \times s^{-1}$, absorbed dose per one exposure - 0.1 mGy) could cause significant changes in the brain bioelectrical activity (Dutov et al. 1989a, b). The changes of every component of auditory and visual EPs (in the form of lower amplitude and latency period lengthening) were observed immediately after the acute radiation syndrome (ARS). The auditory EPs changed proportionally in parallel with the ARS severity: a mild ARS seemed to induce reversible signs of irritation at the level of the brain stem, while moderate and severe syndromes might provoke a growing suppression of its functional activity. After 1-1.5 years following IR exposure, EP changes were revealed, although with a trend towards normalization (Kogan and Chesalin 1989). However, during the remote period of ARS, persistent and pronounced dose-dependent disruption of induced cerebral activity was noted, as shown by the somatosensory, vestibular, auditory and brainstem auditory EPs, which were all characterized by asymmetry, deformation of components and disruption of their amplitude-time

parameters. Indeed, somatosensory EP latency periods in the brain projection and associative areas were increased, and their amplitudes were reduced. The LP of P300 component resulted to be increased and its amplitude reduced, proportionally to the exposure dose. Increased amplitude of the N145 component was also found. Pathological changes in the anterior parts of left hemisphere were discovered during the remote period of ARS, in particular a reduction of the activity of a specific part of somato-sensory afferent system (lemniscus system). Again, the extralemniscus system was abnormally increased, while indicating a dysfunction of the cortex-limbic-reticular complex along with the disturbance of cerebral "sensory gates". The irradiation of thalamic nuclei was found to be associated with the increased amplitude and decreased latency period of the P100 and N145 components, as well as with the increased latency period of P300 component of vestibular EP on rotation chess pattern. These results suggest that a disruption of the central mechanisms of afferent visual system had an impact on cortico-subcortical visual information processing that may be related to possible abnormalities of diencephalic-limbic structures (Loganovsky 1993a, b, c, 1995, 2000a, b, 2002; Yuryev 1995; Nyagu et al. 1994, 1996a, b, 1997, 1999, 2002; Nyagu and Loganovsky 1997; Loganovsky and Loganovskaja 2000; Loganovsky et al. 2005, 2008, 2011).

In other studies, clean-up workers, including the Chernobyl exclusion zone staff, were investigated in the remote period after a low-dose IR exposure of radiations. The ensuing findings based on the somato-sensory, visual, brainstem auditory and auditory EP data analyses, reported an overall dose-dependent impairment of the brain information processes. Somato-sensory EPs were characterized by topographic abnormalities in the left temporo-parietal area. Depending on the exposure doses, the results highlighted an increased contralateral LP, as well as reduced amplitude of contralateral thalamo-cortical N20 and cortical P25 components. Somatosensory EP changes are supposed to reflect IR-induced dysfunctions of the cortico-limbic structures in the left dominant hemisphere. The vestibular EP pattern found in the clean-up workers suggested irritations of the limbic structures along with an impairment of the afferent visual systems and of the cortico-subcortical visual information processing. Again, in Chernobyl clean-up workers, latency period of P1, N2 and P2 components of the vestibular EP resulted to be increased (Nikolenko et al. 1992; Trinus et al. 1995; Nikolenko 1998; Rymar 1999, 2004; Shidlovskaja and Rymar 2000; Zabolotnyi et al. 2000, 2001; Trinus and Klymenko 2003; Trinus 2006).

Different studies carried out in liquidators reported similar alterations (Noshchenko and Loganovsky 1991, 1994; Nyagu et al. 1991, 1992a, b, 1996a, b, 1999, 2002; Loganovsky 1993a, b, c, 1995, 2000a, b, 2002, 2003; Yuryev 1995; Noshchenko 1997; Nyagu and Loganovsky 1997, 1998; Loganovsky and Loganovskaja 2000; Loganovsky et al. 2015). LP increase and amplitude decrease of SSR were also found in the Chernobyl exclusion zone staff and clean-up workers (Vashchenko 1993).

Further, higher mental functions impairment (fatigue, auditory-verbal and visual memory as well as advanced motor functions) and ERP changes were investigated in Chernobyl clean-up workers through auditory ERP registrations using three-stimulus «oddball» paradigm. Amplitude decay of all ERP components (N1, N2 and P3), LP components, N1 and N2 decrement and P3 prolongation were recorded. The most significant latency period differences were found in the frontal areas for N1 and P3 (left hemisphere) and for N2 (right hemisphere). In the liquidators, LP of N1 component had maximum deviations in the frontal left hemisphere. Reduced P300 amplitude was found in all brain areas, in particular, especially in the frontal area of the left hemisphere. The hypothesis of an accelerated brain aging, as a result of low doses of IR in the clean-up workers was also supported by the findings of Zhavoronkova et al. (2010a, b). In particular, the authors reported that retardation of perception, information processing and analysis, as well as poor inhibition and "uneconomical" type of reactivity were related to an impairment of higher mental functions, although these studies had no dosimetry support (Zhavoronkova et al. 2010a, b).

To summarize, the changes of ERPs (and also of EEG) found in the Chernobyl liquidators are very similar to that reported in schizophrenic patients (Loganovsky and Loganovskaja 2000). The shortening of the LP of the early components to all stimuli, regardless of their significance, detected in the liquidators, makes it possible to consider this response as "uneconomical, excessive", and it can be attributed to an impairment of involuntary attention and its reserves due to the weakening of the inhibition processes (Zhavoronkova et al. 2010a, b). Similar alterations have been described also in both elderly persons and patients with different neuropsychiatric conditions (Strelets 1989).

American and Finnish groups found a lengthening of the latency period of the ERP P300 component to auditory stimuli after radiotherapy for a cancer in children and adolescents (Moore et al. 1992, Lähteenmäki et al. 2001), but not in adults (Parageorgiou et al. 2000, Kroczka 2006, Quik 2012), although it should be noted that in these cases the IR doses were high.

Conclusions

The review of the literature would suggest that IR may provoke several multimodal dysfunctions of the human brain sensory systems, particularly, somato-sensory (Loganovsky 1991, 1993a, b, c, 1995; Noshchenko and Loganovsky 1991; Nyagu et al. 1991; Loganovsky 2003), visual (Kogan and Chesalin 1989; Nyagu et al. 1991, 1996; Loganovskaja and Loganovsky 2000; Loganovskaja 2005; Yanovych 2009a), auditory (Kogan and Chesalin 1989; Kozak 1999; Zabolotnyi et al. 2000, 2001; Rymar 2004; Yanovych 2009b; Zhavoronkova et al. 2010a, b, Burtovaya et al. 2013), and vestibular (Nikolenko et al. 1992, Trinus et al. 1995, Yuryev 1995, Trinus 2006, Mishchanchuk 2009), than can be easily detected by ERP. Further dynamic neurophysiological monitoring of individuals from different countries exposed to IR is necessary to support the wide use of this bloodless method for the detection of brain damages. Specific IR dose-dependent changes of the human brain information processing through the assessment of auditory evoked potentials (P300) (Loganovsky and Kuts 2016), appears particularly promising as a marker of early diagnosis of subtle cognitive disorders, but this suggestion requires further replications in larger and heterogeneous samples.

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