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Analiza događajem izazvanih moždanih potencijala kao biomarkera različitih podtipova migrene sa aurom

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REZIME

Uvod: Migrena sa aurom (MwA) je kompleksno neurološko oboljenje koje se karakteriše različitim simptomima osnovnih i viših kortikalnih poremećaja (VKP) tokom napada, ali i suptilnim kognitivnim promenama u interiktalnoj fazi.

Ciljevi: Ciljevi ove studije su: 1) utvrditi sve simptome VKP tokom aure radi pravilnijeg skorovanja kompleksnosti napada, 2) uporediti P3 komponentu između osoba koje imaju MwA i zdravih ispitanika (ZI), kao i da se uporede podgrupe pacijenata, i 3) istražiti N400 efekat kod MwA.

Metodologija: Vizuelna "*oddball*" paradigma koja se sastoji od čestih i retkih stimulusa je korišćena za dobijanje P3 komponente, dok je paradigma koja se sastoji od kongruentnih i nekongruentnih stimulusa korišćena za analiziranje N400 efekta. Amplitude i latencije P3 komponente su upoređivane između grupa i podgrupa. Takođe, uprosečene vrednosti amplituda, pikova, latencija pikova i topografija N400 efekta poređeni su između osoba koje imaju MwA i ZI.

Rezultati: Prisustvo disfazije, kao najčešći VKP, tokom aure može se uzeti kao kriterijum za kompleksan napad i određivanja podgrupe MwA. Kod osoba koje imaju MwA postoji značajno produženje P3 latencije za redak stimulus u odnosu na ZI. Takođe, postoji značajno produženje P3 latencije kod osoba sa kompleksnim napadom u odnosu na osobe koji imaju samo vizuelne simptome. N400 efekat je šire rasprostranjen preko skalpa glave nego kod ZI.

Zaključak: Vizuelna "oddball" paradigma, posebno analiza retkih stimulusa, mogla bi poslužiti kao potencijalno novo sredstvo za precizno profilisanje osoba koje imaju različite kliničke manifestacije napada MwA. N400 efekat može da posluži kao potencijalni metod za proučavanje semantičkog procesiranja informacija kod MwA.

Ključne reči: migrena sa aurom, disfazija, kompleksna aura, P3 komponenta, N400 efekat.

Naučna oblast: medicina

Uža naučna oblast: biomedicinsko inženjerstvo i tehnologije

ABSTRACT

Introduction: Migraine with aura (MwA) is a complex neurological disease characterized by various symptoms of primary and higher cortical disturbances (HCD) during a MwA attack. Also, subtle cognitive changes during the interictal phase are noted.

Objectives: 1) to determine all symptoms of HCD during the aura with an aim to properly address the complexity of the attack, 2) to compare the P3 component between MwA patients and healthy subjects (HSs), as well as to compare MwA subgroups, and 3) to investigate N400 effect in MwA.

Methodology: A visual "oddball" paradigm consisting of frequent and infrequent stimuli was used to obtain the P3 component, while a paradigm consisting of congruent and non-congruent stimuli was used to analyze the N400 effect. The amplitudes and latencies of the P3 component were compared between groups and subgroups. Also, the average amplitudes, peaks, peak latencies and topography of the N400 effect were compared between MwA patients and HSs.

Results: The presence of dysphasia during the aura, as the most common HCD, can be taken as a criterion for complex attack and help in the differentiation of the MwA subgroup. There is a significant P3 latency prolongation in MwA patients for the rare stimulus relative to HSs. Also, there is a significant P3 latency prolongation in patients with a complex attack compared to patients who have only visual symptoms. The N400 effect is more widespread over the scalp than in HSs.

Conclusion: The visual “oddball” paradigm, especially the analysis of rare stimuli, could serve as a potential new tool for accurate profiling of individuals who have different clinical manifestations of MwA attack. The N400 effect can serve as a potential method for studying the semantic processing of information in MwA.

Keywords: migraine with aura, dysphasia, complex aura, P3 component, N400 effect.

Scientific field: medicine

Specific scientific field: biomedical engineering

Sadržaj

1. UVOD

Migrena se svrstava u primarne glavobolje i predstavlja veoma onesposobljavajući poremećaj koji ima jednogodišnju prevalenciju od 15 % u opštoj populaciji (GBD 2016 Neurology Collaborators, 2019). Štaviše, migrena predstavlja prema učestalosti javljanja u opštoj populaciji drugo po redu neurološko oboljenje i doprinosi onesposobljenosti pojedinca u opštoj populaciji više nego sva ostala neurološka oboljenja ukupno (GBD 2016 Neurology Collaborators, 2019; GBD 2016 Neurology Collaborators, 2018). Javlja se tri puta češće kod ženskog pola (Vetvik i MacGregor, 2017). Kod jedne trećine populacije koja boluje od migrene javlja se aura koja najčešće započinje 20-30 minuta pre glavobolje i završava se neposredno pre početka ili tokom glavobolje. Međunarodna klasifikacija za glavobolje označava migrenu sa aurom (MwA) kao oboljenje koje se karakteriše aurom i migrenom (Headache Classification Committee, 2018). MwA je kompleksni i multifaktorijalni neurološki poremećaj čija patogeneza nije u potpunosti razjašnjena. Stoga, trenutno ne postoje specifični neuroradiološki, elektrofiziološki, biohemijski i genetički testovi za postavljanje dijagnoze, zbog čega je klasifikacija i dijagnostika bazirana na opisu kliničkih simptoma.

1.1. Istorijat klasifikacija migrene sa aurom

Prvi opisi MwA datiraju pre više od 2000 godina, kada je Hipokrat zabeležio da je migrena periodičan sindrom kome prethodi aura i koji se karakteriše glavoboljom koja zahvata polovinu glave i da su tokom glavobolje često prisutni gastrointestinalni simptomi: "*He seemed to see something shining before him like a light, usually in part of the right eye; at the end of a moment, a violent pain supervened in the right temple, then in all the head and neck....vomiting, when it became possible, was able to divert the pain and render it more moderate*" (Pearce, 1986).

Još sredinom 20-og veka uočeno je da nedostaje detaljnija podela glavobolja prema uzroku nastanka i načinu manifestacije. Međutim, tek 1988. godine objavljena je Prva međunarodna klasifikacija za glavobolje koju je osmislio Komitet za klasifikaciju glavobolja predvođen profesorom Jes Oleson-om ispred Međunarodnog udruženja za glavobolje. Po prvi put glavobolje su klasifikovane na primarne i sekundarne (Headache Classification Committee, 1988). Primarne glavobolje se definišu kao glavobolje koje nisu izazvane nekim oboljenjem, dok se sekundarne glavobolje definišu kao novonastale glavobolje koje se javljaju zajedno sa nekim drugim poremećajem koji može izazvati glavobolju (Headache Classification Committee, 1988). Prema Prvoj međunarodnoj klasifikaciji za glavobolje, u primarne glavobolje se svrstava: migrena, glavobolja tenzionog tipa, klaster glavobolja i ostale primarne glavobolje (Headache Classification Committee, 1988). Presudnu ulogu u klasifikaciji primarnih glavobolja imale su kliničke manifestacije glavobolja, pa se tako migrena definisala kao primarna glavobolja koja se karakteriše rekurentnim napadima glavobolje različitih inteziteta i trajanja, pulsirajućeg kvaliteta bola, javljajući se unilateralno zahvatajući određenu površinu glave i često praćena mučninom i fotofobijom (Headache Classification Committee, 1988). U Prvoj međunarodnoj klasifikaciji za glavobolje, migrena ima dva osnovna podtipa: migrena bez aure i migrena sa aurom. Iako je Prva međunarodna klasifikacija za glavobolje donela važne smernice za postavljanje dijagnoze i terapiju migrene, ostale su mnogobrojne nedoumice u svakodnevnoj kliničkoj praksi.

Do neophodnih promena u klasifikaciji migrena dolazi tek 2004. godine kada je objavljena Druga međunarodna klasifikacija za glavobolje (International Headache Society Classification Subcommittee, 2004). Najvažnija promena odnosila se na MwA koja je klasifikovana na dodatne podtipove: tipičnu auru sa migrenskom glavoboljom, tipičnu auru sa ne-migrenskom glavoboljom, tipičnu auru bez glavobolje, familijarnu hemiplegičnu migrenu, sporadičnu hemiplegičnu migrenu i

bazilarnu migrenu (International Headache Society Classification Subcommittee, 2004). Takođe, uveden je i pojam hronične migrene koja se postavljala kao dijagnoza ukoliko osoba ima više od 15 dana u mesecu migrenu tokom najmanje 3 meseca (Olesen, 2008). Zatim, omogućeno je da osoba ima više dijagnoza glavobolja ukoliko je to potrebno, kao što je u slučaju kad osoba ima primarno MwA, a zatim usled nekog drugog poremećaja počnu da se javljaju i drugi oblici glavobolja ili osoba ima i migrenu bez aure.

Treća međunarodna klasifikacija za glavobolje objavljena je 2018. godine (Headache Classification Committee, 2018). S obzirom da je početkom 21. veka došlo do značajnog tehnološkog napretka u oblasti medicinsih tehnologija i da je sve veći broj relevantnih kliničkih i naučnih centara uključeno u istraživanje primarnih glavobolja, dolazi se do značajnih otkrića u oblasti patogeneze i terapije MwA, zbog čega je postalo važno korigovati kriterijume za dijagnozu i uvrstiti nove podtipove MwA (Charles, 2018). U trećoj međunarodnoj klasifikaciji za glavobolje MwA se klasifikuje na sledeće podtipove: migrena sa tipičnom aurom, migrena sa aurom moždanog stabla, hemiplegična migrena i retinalna migrena (Headache Classification Committee, 2018). Kriterijumi za postavljanje dijagnoze "migrena sa aurom" su sledeći: 1) da je osoba imala dva ili više ataka koji ispunjavaju kriterijume za postavljanje dijagnoze; 2) prisustvo jednog ili više potpuno reverzibilnog simptoma aure koji nastaju usled fokalnih poremećaja cerebralnog korteksa ili moždanog stabla; i 3) prisustvo najmanje dve od četiri karakteristike: najmanje jedan simptom u auri koji postepeno progredira i traje duže od pet minuta ili više simptoma u auri koji se javljaju sukcesivno; da svaki pojedinačan simptom traje 5-60 minuta; da je najmanje jedan simptom unilateralan i da se glavobolja javlja tokom ili neposredno nakon aure (Headache Classification Committee, 2018). Svaki od podtipova MwA dobija specifične dodatne kriterijume za postavljanje dijagnoze. Dodatni kriterijumi za "migrena sa tipičnom aurom" su sledeći: 1) da osoba tokom aure ima vizuelne, somatosenzorne i/ili disfazične simptome; i 2) da osoba tokom aure nema simptome poremećaja motornog sistema, moždanog stabla i/ili retinalne simptome aure. Simptomi poremećaja moždanog stabla su: dizartrija (jasno razlikovana od disfazičnih simptoma), vertigo, tinitus, hipakuzija, diplopija, ataksija, i smanjen nivo svesti (Glazgovski koma skora ≤13). Retinalna migrena je definisana kao monokularni vizuelni "pozitivni" ili "negativni" simptomi koji su u potpunosti reverzibilni i nisu nastali usled oštećenja struktura oka. Klasifikacija i kriterijumi za dijagnozu hemiplegične migrene su najviše korigovani od svih ostalih podtipova migrene. Kod familijarnog podtipa hemiplegične migrene utvrđena su četiri podtipa prema genetičkim mutacijama koje su detektovane: 1) familijarna hemiplegična migrena tip 1 (CACNA1A), familijarna hemiplegična migrena tip 2 (ATP1A2), familijarna hemiplegična migrena tip 3 (SCN1A) i familijarna hemiplegična migrena tip 4 (testiranja nisu pokazala mutacije na CACNA1A, ATP1A2 i SCN1A genima).

U toku su promišljanja o četvrtoj verziji klasifikacije glavobolja gde preovladava mišljenje da je potrebno prilagoditi klasifikaciju i kriterijume za postavljanje dijagnoze prema rezultatima kliničkih studija i zaključcima baziranim na jasnim i nedvosmislenim dokazima, a ne samo na osnovu mišljenja grupe eksperata u oblasti glavobolja (Ashina i sar, 2021). Štaviše, prethodne i trenutna međunarodna klasifikacija za glavobolje se baziraju uglavnom na kliničkim kriterijumima. Nedostatak ovakve metodologije jeste što se u potpunosti ne obuhvata i ne prepoznaje heterogenost migrene, a zatim i ne prepoznaje važnost neurobioloških faktora u ovoj bolesti. Usled sve većeg broja otkrivenih biomarkera postepeno se popravlja karakterizacija bolesti i otkrivaju novi načini za lečenje MwA (Ashina i sar, 2021).

1.2. Faze napada i patofiziloški mehanizmi kod migrene sa aurom

MwA se sastoji od pet faza: prodromalna faza, aura, glavobolja, postdromalna faza i interiktalna faza.

Akutni napadi MwA zavise od individualnih i urođenih predispozicija ka osetljivosti na različite faktore koji mogu da pokrenu napad. Među najčešćim faktorima koji mogu da izazovu napad MwA su: hrana, fizički napor, jaki mirisi (npr. parfemi), duvanski dim, promena glikemije, deprivacija sna, poremećaj homeostaze u organizmu, emocionalni stres, jaka svetlost ili zvuk, dehidratacija i promena vremenskih uslova (Al-Shimmery, 2010; Amin i sar, 2018Karsan i sar, 2021). Napad može nastati nekoliko minuta od izloženosti nekom od prethodno navedenih faktora, a može se javiti i posle nekoliko dana (Karsan i sar, 2021). U tom periodu mogu se javiti prodromalni simptomi koji označavaju prodromalnu fazu napada. Prodrmalna faza napada se definiše kao pojava simptoma koji nastaju 2-48 časova pre aure (Headache Classification Committee, 2018). Najčešći prodromalni simptomi su: zevanje, zamor, poremećaj koncentracije, promena raspoloženja, osećaj gladi ili potreba za nekom namirnicom, preosetljivost na svetlost i buku, nelagodan osećaj u vratnim mišićima i letargija (Schoonman i sar, 2006; Laurell i sar, 2016). Patofiziološki mehanizmi koji dovode do ovih simptoma nisu u potpunosti razjašnjeni, ali se njihov nastanak dovodi u vezu sa prolaznim poremećajem funkcije hipotalamusa i dopaminergičkog sistema u limbičkim strukturama (Akerman i Goadsby, 2007; Alstadhaug, 2009).

Posle prodromalne faze, kod napada MwA, javlja se aura. Aura se definiše kao fokalni neurološki simptomi koji najčešće traju do 60 minuta (Headache Classification Committee, 2018). Vizuelni simptomi su najčešći simptomi kod migrene sa tipičnom aurom (Headache Classification Committee, 2018). Vizuelni simptomi se mogu javiti pojedinačno ili više simptoma istovremeno i mogu zahvatiti periferni i centralni deo vidnog polja (Viana i sar, 2017). Pojava ovih simptoma može da varira od napada do napada (Hansen, Goadsby i Charles, 2016). Klasični vizuelni simptomi se manifestuju kao svetlaci ili ispadi u vidnom polju ili kao nepravilne svetlucajuće linije (Eriksen et al, 2005). Mogu se javiti i kompleksniji vizuelni fenomeni kao što su: poremećaji vizuelne percepcije, pojava klasičnih simptoma praćenih višebojnim spektrom, mikropsija, makropsija, palinopsija i prosopagnozija (Sandor i sar, 2004; Belcastro i sar, 2011; Queiroz i sar, 2011; Petrusic i sar, 2013; Viana i sar, 2016).

Pored vizuelnih simptoma, tokom aure često se javljaju i senzitivni simptomi kao što su: trnjenje ili utrnulost prstiju, šake, ruke, lica, jezika i ponekad nekog drugog dela tela (Russell i Olesen, 1996; Petrusic i sar, 2019a). Pojava senzitivnih simptoma može biti praćena i dispraksijom, astereognozijom i osećajem da neki deo tela ne pripada toj jedinki (Petrusic i sar, 2019a). Ovakvi simptomi pripadaju višim kortikalnim poremećajima i nastaju usled disfunkcije polimodalnih asocijativnih područja cerebralnog korteksa koji učestvuju u integraciji senzornih informacija različitih modaliteta (Petrusic i sar, 2013). Od viših kortikalnih poremećaja kod MwA mogu da se jave još i različiti oblici disfazije (npr. disnomija ili zamena reči u rečenici ili slova u reči) i poremećaji memorije (Russell i Olesen, 1996; Vincent i Hadjikhani, 2007; Petrusic i sar, 2013; Petrusic i sar, 2014).

Široki spektar simptoma tokom aure i njihova promenljivost u intezitetu i vremenu trajanja kod iste osobe sugerišu veoma kompleksne patogenetske mehanizme koji zahvataju različite delove centralnog nervnog sistema i utiču na autonomne, afektivne, kognitivne i senzorne funkcije (Burstein i sar, 2015). Iako, u potpunosti nisu razjašnjeni patogenetski mehanizmi koji dovode do napada MwA, ustanovljeno je da se tokom aure javlja talas kortikalne depolarizacije, ekscitirajući neurone i glijalne ćelije, koji posle primarne ekscitacije dovodi do supresije spontane neuronske aktivnosti (Charles i Brennan, 2009). Iako je ova hipoteza postavljena još sredinom 20-og veka

(Lashley, 1941; Milner, 1958), na osnovu prethodnog saznanja da se kod eksperimentalnih životinja može izazvati elektrofiziološki fenomen koji se karakteriše hiperekcitabilnošću neurona koja se širi od okcipitalnog režnja ka parijetalnom i temporalnom režnju brzinom od 3-4 mm/minuti i posledičnom depresijom aktivnosti specifičnih kortikalnih regija (Leao, 1944; Dahlem i Hadjikhani, 2009), tek 2001. godine je vizuelizovan fenomen šireće kortikalne depolarizacije / depresije tokom faze aure u napadu MwA (Hadjikhani i sar, 2001). Teorija o širećoj kortikalnoj depolarizaciji / depresiji i danas predstavlja osnov za tumačenje nastanka faze aure i posledično fazu glavobolje kod MwA iako ova teorija ima brojne nelogičnosti (McComas i Upton, 2015; Goadsby i sar, 2017; Vuralli i sar, 2021). Jedna od bitnih nelogičnosti jeste redosled javljanja simptoma i njihovo trajanje; na primer, pojava prvo senzitivnih simptoma ili istovremeno javljanje vizuelnih i senzitivnih simptoma osporava ovu teoriju ukoliko se smatra da talas šireće kortikalne depolarizacije počinje u okcipitalnom režnju i zatim se širi rostralno brzinom od 3-4 mm/minuti (Petrusic i Zidverc-Trajkovic, 2014). Ipak, ovakve nelogičnosti mogu se objasniti time da talas šireće kortikalne depolarizacije može započeti na različitim mestima u cerebralnom korteksu simultano ili čak da su u pojedinim napadima MwA subkortikalne strukture centralnog nervnog sistema mesta gde se talas šireće depolarizacije javlja i širi ka cerebralnom korteksu (Kunkler i Kraig, 2003 Petrusic i Zidverc-Trajkovic, 2014). Takođe, jedna od bitnih nelogičnosti jeste što se ponekad javljaju samo vizuelni simptomi, a ponekad dodatno i različiti poremećaji viših kortikalnih funkcija kod iste osobe. Pažljivo praćenje ovih simptoma i korelacija sa nalazima na naprednim uređajima za neurovizuelizaciju mogu u budućnosti razjasniti ovakve nelogičnosti.

Jedan od načina praćenja i procene složenosti napada tipične MwA jeste nedavno razvijen sistem za skorovanje kompleksnosti migrenske aure (*Migraine Aura Complexity Score* - MACS) (Petrusic i sar, 2019a). Na vrednost skora utiču tri faktora: 1) teoretska površina zahvaćenosti primarnog vizuelnog i somatosenzornog korteksa pretpostavljena procenom zahvećenosti vidnog polja vizuelnom aurom i zahvaćenosti delova tela senzitivnom aurom, 2) javljanje trnjenja ruke i/ili dela glave i 3) javljanje viših kortikalnih poremećaja (npr. disfazija, dispraksija, amnezija, dismorfia, itd.). MACS može da varira od 0 poena (kad osoba ima samo vizuelnu auru koja zahvata samo četvrtinu vidnog polja) do 9 poena (kad osoba ima vizuelnu auru koja zahvata više od polovine vidnog polja i praćena je trnjenjem ruke i lica, kao i pojavom disfazije ili nekog drugog višeg kortikalnog poremećaja) (Petrusic i sar, 2019a). Detaljan prikaz skorovanja je prikazan u Tabeli 1. Napad MwA koji ima MACS $\geq$ 4,5 poena može da se označi da predstavlja kompleksnu MwA (Petrusic i sar, 2019b). MACS se može upotrebiti za procenu kompleksnosti aure u toku pojedinačnog napada, a može se koristiti i za sveobuhvatnu procenu više napada kod iste osobe tako što se izračuna prosečna vrednost MACS od svih zabeleženih napada kod iste osobe (Petrusic i sar, 2019a). Glavni cilj ovog skora jeste da se omogući detaljnije i homogenije grupisanje osoba koje boluju od MwA kako bi se omogućila klinička i neurovizuelizaciona ispitivanja podgrupa kod tipične MwA.

Tabela 1. Prikaz skorovanja kompleksnosti tipične migrenske aure koristeći *Migraine Aura Complexity Score* - MACS

Migraine Aura Complexity Score - MACS (0-9 poena)	
Skorovanje prema javljanju senzitivnih simptoma na ruci i/ili glavi (0-2 poena):	
Nema senzitivnih simptoma	0
Pojava senzitivnih simptoma na ruci	1
Pojava senzitivnih simptoma na površini glave	1
Skorovanje teoretske zahvaćenosti površine primarnog vizuelnog i somatosenzornog korteksa (0-2 poena):	
Neznačajna zahvaćenost primarnog vizuelnog korteksa (manje od polovine vidnog polja)	0
Značajna zahvaćenost primarnog vizuelnog korteksa (polovina ili više od polovine vidnog polja)	1
Značajna zahvaćenost primarnog somatosenzitivnog korteksa (glava, ruka i noga)	1
Skorovanje pojave viših kortikalnih poremećaja (0-5):	
Ne javljaju se viši kortikalni poremećaji	0
Javljaju se viši kortikalni poremećaji koji su u vezi sa vizuelnim korteksom	1
Javljaju se viši kortikalni poremećaji koji su u vezi sa somatosenzitivnim korteksom	2
Javljaju se simptomi disfazije i/ili amnezije tokom aure	2

Faza glavobolje uglavnom započinje posle završetka aure, mada simptomi aure mogu perzistirati i tokom glavobolje. Glavobolja se tipično karakteriše unilateralnim bolom pulsirajućeg karaktera koji je često udružen sa pojavom mučnine i preosetljivošću na svetlost, mirise i zvukove (Headache Classification Committee, 2018). Ukoliko se glavobolja ne tretira može trajati i do 72 sata (Headache Classification Committee, 2018). Najprihvaćeniji model objašnjenja nastanka migrenozne glavobolje jeste da talas šireće depolarizacije stimuliše V kranijalni nerv i aferentne meningealne nerve što dovodi do njihove neurogene inflamacije i posledične vazodilatacije u tvrdoj moždanici (Moskowitz, 1993; Zhang et al, 2010; Charles i Baca, 2013). Inflamacije trigeminovaskularnog sistema može dovesti do centralne senzibilizacije, što može biti uzrok nastanka refraktornih glavobolja i čestih napada migrene (Burstein et al, 2015). Posle prestanka glavobolje javlja se postdromalna faza koja traje 24-48 sati i karakteriše se iscrpljenošću, pospanošću, otežanom koncentracijom i promenom raspoloženja (Giffin i sar, 2016). Period kada osoba nema nikakve simptome koji su u vezi sa prethodnim fazama MwA naziva se interiktalna

faza. Većina studija se upravo sprovodi tokom interiktalne faze, jer je dizajn studije koji uključuje ispitivanje osoba tokom ostalih faza teško organizovati. Ipak, brojni rezultati ukazuju da postoje strukturne i funkcionalne promene centralnog nervnog sistema tokom interiktalne faze kod osoba koje boluju od MwA, kao i da postoje razlike između podgrupa (Evers i sar, 1997; Schoenen, 2006; Datta i sar, 2013; Coppola i sar, 2013; Cosentino, Fierro i Brighina, 2014; Chong, Schwedt i Dodick, 2016; Petrusic i sar, 2019b; Coppola sar, 2021). Svakako, MwA pruža izvanrednu priliku za proučavanje organizacije funkcionisanja cerebralnog korteksa (Petrusic i sar, 2014).

1.3. Elektrofiziološke tehnike i migrena sa aurom

U proteklih 50 godina, veliki broj studija je posvećen istraživanju neurofizioloških procesa koji mogu dovesti do predispozicije nastanka napada migrene (Coppola i sar, 2019). U literaturi su prijavljeni različiti elektrofiziološki pokazatelji da tokom interiktalne faze postoje razlike između osoba koje imaju migrenu i zdravih osoba koje ne boluju od migrene (Coppola i sar, 2005; Coppola i sar, 2007; Rauschel i sar, 2016; Kalita i sar, 2018). Međutim, ove studije uglavnom nisu uzimale u obzir specifične razlike u patofiziologiji migrene sa i bez aure, zato što je teško regrutovati za studiju dovoljan broj osoba koje imaju MwA i zato što se smatralo da je i kod jedne i kod druge grupe ispitanika u osnovi isti neurofiziološki poremećaj (Purdy, 2008). Poslednjih godina se ovaj stav značajno menja u naučnoj zajednici koja se bavi istraživanjem primarnih glavobolja, ukazujući na kompleksnije patofiziološke mehanizme kod MwA u odnosu na migrenu bez aure (Szabó i sar, 2018; Coppola i sar, 2019; Petrusic i sar, 2019b). Svakako, elektrofiziološke tehnike mogu biti veoma korisne za istraživanje patofizioloških karakteristika MwA i u otkrivanju markera podtipova MwA (Magis, Lisicki i Coppola, 2016; Coppola i sar, 2019).

1.3.1. Elektroencefalografija (EEG)

Abnormalan EEG nalaz je češći u populaciji osoba koji boluju od migrene u odnosu na zdravu populaciju, iako ne postoji specifičan EEG nalaz koji bi ukazao da neko boluje od migrene (Martinović, 2006). Tokom interiktalne faze kod osoba koje imaju MwA, kvantativna analiza spontanog EEG zapisa ukazala je na postojanje povećanih amplituda alfa talasa u okcipatalnoj regiji mozga (Facchetti i sar, 1990), kao i šire rasprostranjena pojačana ukupna snaga delta (Genco i sar, 1994) i teta (Facchetti i sar, 1990; Genco i sar, 1994) talasa u odnosu na zdravu grupu ispitanika. Takođe, pronađena je i redukcija alfa i teta talasa na kontralateralnoj strani u odnosu na neurološke simptome (Schoenen, Jamart i Delwaide, 1987; Neufeld i sar, 1991). Tokom prodromalne faze primećeno je da postoji povećana asimetrija alfa i teta talasa u hemisferama (Bjørk M i Sand, 2008).

1.3.2. Vizuelno evocirani potencijali (VEP) mozga

Neurofiziološke studije su pokazale da se često registruje hiperekscitabilnost cerebralnog korteksa i poremećaj habituacije kod osoba koje imaju MwA (Coppola i sar, 2019). Takođe, pokazano je da je potreban manji intezitet transkranijalne magnetne stimulacije vizuelnog korteksa kod osoba koje imaju MwA u odnosu na zdrave ispitanike (Young i sar, 2004). Štaviše, različiti tipovi stimulusa, kao što su vizuelni, senzitivni ili auditivni, ukazuju na abnormalnosti senzornih neuromreža kod osoba koje imaju MwA (Coppola i sar, 2019).

VEP imaju ulogu u proceni strukturnog i funkcionalnog integriteta vizuelnih puteva od retine do okcipitalnog korteksa. Imajući na umu da su vizuelni putevi u centralnom nervnom sistemu blisko u vezi sa patofiziološkim mehanizmima MwA (Granziera i sar, 2006; Datta i sar, 2013; Lisicki i sar, 2018), VEP mogu poslužiti za ispitivanje poremećaja vizuelnog procesiranja kod osoba koje boluju od MwA i za istraživanje patofizioloških mehanizama koji ove osobe

razlikuje od osoba koje imaju migrenu bez aure (Yilmaz i sar, 2001; Boćkowski i sar, 2003; Jancic i sar, 2016). Štaviše, istraživanja sugerišu i da osobe koje imaju kompleksniji napad MwA (imaju i nevizuelne simptome, kao što je disfazija) kao odgovor na vizuelne stimuluse imaju i veće N1-P1 amplitude evociranih potencijala u odnosu na osobe koje imaju samo vizuelne simptome tokom napada MwA (Coppola i sar, 2015).

U mnogobrojnim istraživanjima, VEP pokazuje brz porast N1-P1 i P1-N2 amplituda pri svakom tipu svetlosne stimulacije i karakteriše se poremećajem habituacije pri ponovnoj stimulaciji (Afra i sar, 1998; Rauschel i sar, 2016; Kalita i sar, 2018). Habituacija predstavlja bihejvioralni odgovor smanjenja kortikalne aktivnosti usled repetitivne stimulacije koji se ne javlja zbog zamora receptora koji su podraženi stimulacijom (Rankin i sar, 2009). Uloga habituacije jeste da spreči preopterećenje informacijama u senzornim regijama cerebralnog korteksa (Thompson, 2009). Izostanak habituacije kod osoba koje imaju MwA se objašnjava pojavom talamokortikalne disaritmije (Coppola i sar, 2007). Štaviše, poremećaj procesiranja vizuelnih informacija se menja tokom faza migrene, tako što se promene na VEP naglašavaju tokom interiktalne faze ili tokom prodromalne faze (Coppola i sar, 2013; Coppola i sar, 2015) i atenuiraju tokom napada MwA (Judit, Sandor and Schoenen, 2000; Coppola i sar, 2013) ili posle uzimanja leka (Ince, Erdogan-Bakar and Unal-Cevik, 2017).

1.3.3. Somatosenzorno evocirani potencijali (SSEP) mozga

SSEP se uglavnom koriste kako bi se na objektivan način procenila funkcionalnost senzitivnog sistema, počevši od perifernih nervih puteva, preko kičmene i produžene moždine, do talamusa i senzitivnog cerebralnog korteksa. Pregledom literature uočava se da SSEP u studijama o migreni nisu dovoljno korišćeni za ispitivanje patogeneze i za klasifikaciju podtipova migrene. Takođe, nedostatak većine studija koje su uključivale SSEP u dizajn jeste nedovoljan broj ispitanika i loša homogenizacija ispitivanih grupa (prema trajanju i kvalitetu simptoma koji se javljaju kod osoba koje imaju migrene sa aurom) (Zhu, Coppola i Shoaran, 2019).

U većini studija, amplitude i latencije dobijene posle stimulacije nervusa medianusa nisu se značajno razlikovale između osoba koje imaju migrenu, ali se nalaze u interiktalnoj fazi, i zdravih ispitanika (Montagna i sar, 1985; Firenze i sar, 1988; De Tommaso i sar, 1997; Ozkul Y i Uckardes, 2002; Sakuma i sar, 2004; Coppola i sar, 2005). Međutim, zapaženo je da postoji poremećaj somatosenzorskog procesiranja informacija, kao i poremećaj habituacije, kod osoba koje imaju migrenu i da postoji korelacija između težine bolesti i stepena poremećaja habituacije (Restuccia i sar, 2013; Kalita J, Bhoi SK and Misra, 2014; Restuccia i sar, 2014). Kao i kod VEP, ovakvi poremećaji habituacije mogu se objasniti smanjenom sposobnošću lateralne inhibicije u funkcionalno odgovornoj zoni cerebralnog korteksa (somatosenzorni korteks) koja je blisko u vezi sa postojanjem talamokortikalne disaritmije (Coppola i sar, 2007). Takođe, kao i kod studija koje su koristile VEP, pronađena je značajna asimterija između dve hemisfere (De Tommaso i sar, 1997).

Detaljnije istraživanje mehanizama talamokortikalne disaritmije kod osoba koje imaju MwA ili migrenu bez aure pokazalo je da postoje promene u ranim komponentama visoko frekventih oscilacija sadržanih u odgovoru na somatosenzorne stimuluse (Coppola i sar, 2005). Detektovane promene se objašnjavaju kao poremećaj transmisije u talamokortikalnim holinergičkim vlaknima bele mase cerebruma (Coppola i sar, 2005). U kasnim komponentama visoko frekventih oscilacija (450-750 Hz) sadržanih u odgovoru na somatosenzorne stimuluse nisu detektovane značajne promene između osoba koje imaju MwA i zdravih ispitanika, što je objašnjeno kao očuvanost GABA-ergičkih vlakana u intrakortikalnoj somatosenzornoj regiji cerebruma kod osoba koje imaju MwA (Mochizuchi i sar, 2003; Coppola i sar, 2005). Ono što je zanimljivo jeste da tokom napada migrene nije detektovana značajna razlika u amplitudama visoko frekventih oscilacija sadržanih u

odgovoru na somatosenzorne stimuluse, što podržava prethodne studije u kojima je pokazano da tokom napada dolazi do uspostavljanja normalne habituacije (Restuccia i sar, 2014). Coppola i saradnici (Coppola i sar, 2005), dalje sugerišu da ovi rezultati ukazuju na to da osobe koje imaju migrenu nemaju hiperekscitabilni korteks, niti poremećaj u funkciji intrakotikalnih inhibitornih neurona, već da postoji smanjena preaktivnost ekscitovanja senzornih delova cerebralnog korteksa. Prema ovoj teoriji, inicijalno nastaje slabiji odgovor na somatosenzorne stimuluse i potrebno je više vremena da ekscitacija dovede do aktivacije inhibitornih neurona, tj. do nastanka habituacije (Coppola i sar, 2005). Takođe, postoje elektrofiziološki dokazi, dobijeni somatosenzornim stimulusima, da je u patofiziološke mehanizme migrene uključena i produžena moždina pored talamusa (Porcaro i sar, 2017).

Pored proučavanja patogenetskih mehanizama MwA, SSEP, kao praktična i neinvazivna tehnika, može da se koristi i za predikciju faze u kojoj se nalazi osoba koja boluje od MwA (Zhu, Coppola and Shoaran, 2019; Fu-Jung i sar, 2022). Pokazano je da postoje ciklične promene u ekscitaciji neurona u produženoj moždini i u somatosenzornom korteksu, kao i da su u patofiziološke mehanizme uključeni i ekscitatorni i inhibitorni neuroni (Fu-Jung i sar, 2022). Takođe, utvrđeno je da pik ekscitabilnosti se postiže u prodromalnoj fazi, ranije u produženoj moždini, a zatim i u somatosenzoroj regiji cerebralnog korteksa, što je u skladu sa hipotezom da produžena moždina ima važnu ulogu u patogenezi migrene (Fu-Jung i sar, 2022).

1.3.4. Događajem izazvani kortikalni potencijali (ERP)

Događajem izazvani potencijali (engl. *event related potentails* - ERP) mozga predstavljaju pouzdanu i neinvazivnu metodu za ispitivanje neurofizioloških procesa koji mogu da ukažu na suptilne promene u mozgu koje se javljaju tokom učestvovanja u rešavanju zadataka koji zahtevaju aktivaciju kognitivnih procesa (Patel i Azzam, 2005). ERP se sve češće koristi kao biomarker u različitim neurološkim oboljenima (Polich, 2007). Najistraživanija komponenta ERP jeste P3 komponenta, koja predstavlja pozitivan odgovor koji se javlja posle adekvatnog stimulusa u intervalu od 250-500 milisekundi - P300 komponenta ERP (Polich, 2007). P300 odgovor nastaje kada osoba ima zadatak da donese odluku i paradigma se najčešće dizajnira tako da je osoba izložena nasumičnim čestim i retkim stimulusima (paradigma neočekivanog stimulusa, engl. *oddball paradigm*) pri čemu ima zadatak da prijave retke stimuluse kada ih vidi ili čuje (Polich, 2007). Pored procene kognitivnih procesa u različitim neurološkim oboljenjima (Braverman i Blum, 2003), P300 se može koristiti kao tehnika za detektovanje neistina tokom ispitivanja ili za upravljanje interfejsom mozak-računar (engl. *brain-computer interfacing* - BCI) kod osoba koje boluju od paralize izazvane različitim oboljenjima (Farwell LA i Smith, 2003; Piccione i sar, 2006; Nijboer i sar, 2008).

U literaturi ne postoje konzistentne razlike u karakteristikama P3 komponente između pacijenata koji imaju migrenu, druge tipove primarnih glavobolja i zdravih ispitanika (Schoenen i sar, 1989; Evers i sar, 1998; Chen i sar, 2007). Nekoliko studija koje su koristile ERP u svom dizajnu su pokazale da su kod pacijenata koji boluju od migrene zabeležene smanjene amplitude P3 komponente (Wang, Schoenen i Timsit-Berthier, 1995; Chen i sar, 2007), dok u drugim studijama je zabeleženo da su amplitude povećane i da je latencija P3 komponente produžena kod pacijenata koji imaju migrenu (Mazzotta i sar, 1995; Evers i sar, 1997; Titlic i sar, 2015; Huang i sar, 2017). Suprotni nalazi u prethodnim studijama mogu biti objašnjeni različitim kriterijmima za regrutovanje pacijenata koji su u različitim fazama ciklusa migrene ili pripadaju različitim fenotipovima migrene (MwA ili migrena bez aure ili čak različiti podtipovi MwA) (de Araújo i sar, 2012). Takođe, važan nalaz u studijama jeste i da postoji poremećaj habituacije tokom sprovođenja kognitivnih zadataka kod osoba koje imaju migrenu, dizajniranih kao paradigme neočekivanog vizuelnog stimulusa koje

su se sastojale od čestih (85 % bljeskova bele svetlosti) i retkih (15 % bljeskova crvene svetlosti) stimulusa (Evers i sar, 1997; Evers i sar, 1998).

Iz svega prethodno navedenog, a i iz mnogobrojnih neuropsiholoških studija (Lo Buono i sar, 2017; Vuralli, Ayata i Bolay, 2018), može se zaključiti da osobe koje imaju migrenu, posebno osobe koje boluju od MwA, mogu imati suptilan kognitivni poremećaj tokom interiktalne faze. Najčešće kognitivne razlike u odnosu na zdrave ispitanike pronađene u neuropsihološkim studijama su poremećaj vizuelne i verbalne memorije, smanjena brzina obrađivanja informacija, egzekutivna disfunkcija i poremećaj pažnje (Evers i sar, 1997; Mulder i sar, 1999). Međutim, nije poznato da li su ove promene u korelaciji sa kompleksnošću migrenske aure, jer studije sprovedene na homogenoj grupi pacijenata koji imaju tipičnu auru su retke i ne postoje poređenja između podgrupa MwA u smislu kompleksnosti migrenske aure. Svakako, istraživanja u ovoj oblasti sugerišu da hiperekscitabilni vizuelni korteks kod MwA nije samo uzročno-posledično povezan sa poremećajima u multisenzorskom procesuiranju informacija, već da postoje i poremećaji u kognitivnim procesima koji se beleže tokom interiktalne faze.

Jedan od često potcenjenih fenomena koji se javlja tokom aure jeste javljanje poremećaja govora u različitim oblicima kao što su: disnomija, usporen govor, nerazumljiv govor, nerazumevanje tuđeg govora, itd. (Russell i Olesen, 1996; Petrusic i sar, 2013). Jedan od mogućih načina proučavanja poremećaja semantičkog procesiranja informacija u određenim regijama mozga jeste analiziranje N400 ERP komponente (Kutas i Federmeier, 2011). Komponenta N400 se može analizirati primenom zadatka semantičkog odlučivanja koristeći u paradigmama semantički prajming, gde je ciljna reč bila ili nije bila na neki način povezana sa prethodnom (osnovnom) rečju ili slikom. U poređenju sa kongruentnim stanjem u kojem su reči i objekti sa slike ispravno povezani, kod nekongruentnog stanja reči i objekti sa slike se ne poklapaju što dovodi do pojave N400 komponente koja ima negativnu amplitudu koja dostiže pik oko 300-500 milisekundi posle stimulacije sa najvidljivijim efektom na centro-parijetalnim elektrodama (Kutas i Hillyard, 1980). Prednost ove tehnike je u tome što obezbeđuje trenutni i kontinuirani zapis neurofizioloških procesa povezanih sa kognitivnom obradom stimulusa sa visokom temporalnom rezolucijom, čime ERP tehnika omogućava precizno i objektivno merenje prostornih i vremenskih sekvenci elektrofizioloških odziva na stumuluse na kortikalnom nivou, direktno povezanih sa različitim procesima koji su u osnovi semantičke memorije (Eddy, Schmid i Holcomb, 2006).

Bolja karakterizacija kliničkih i elektrofizioloških fenotipova MwA može dovesti do boljeg klasifikovanja pacijenata i posledično omogućiti personalizovano prilagođenu terapiju i dovesti do novih pravaca u tretmanu osoba koje imaju različite podtipove MwA (Coppola i sar, 2019).

2. CILJEVI ISTRAŽIVANJA I HIPOTEZE

Ciljevi doktorske disertacije su:

1) Analiza simptoma migrenske aure sa ciljem klasifikovanja pacijenata u podgrupu koju čine osobe sa ne-kompleksnim simptomima (bez poremećaja viših kortikalnih funkcija tokom napada migrene sa aurom) i podgrupu koju čine osobe sa kompleksnim simptomima (prisutni poremećaji viših kortikalnih funkcija tokom napada migrene sa aurom) migrenske aure.

2) Poređenje P300 komponente događajem izazvanih kortikalnih potencijala (ERP) merenih elektoencefalografski (EEG) između osoba koje imaju migrenu sa aurom i zdravih ispitanika.

3) Poređenje N400 komponente događajem izazvanih kortikalnih potenicijala između osoba koje imaju migrenu sa aurom i zdravih ispitanika.

4) Ispitivanje uticaja kompleksnosti aure na komponente događajem izazvanih kortikalnih potencijala.

Hipoteze koje su dovele do doktorske disertacije su:

1) Prva radna hipoteza je da između osoba koje imaju migrenu sa aurom i zdravih ispitanika postoji razlika u kognitivnom procesuiranju koja se može detektovati uz pomoć P300 komponente.

2) Druga radna hipoteza je da između osoba koje imaju migrenu sa aurom i zdravih ispitanika postoji razlika u N400 komponentama u zavisnosti od tipa stimulusa (kongruetni i nekongruentni).

3) Treća radna hipoteza je da kompleksnost migrenske aure korelira sa promenom u ERP odzivima.

3. REZULTATI

3.1. Studija I - Pregled literature o simptomima koji ukazuju na kompleksan napad migrene sa aurom (Prilog I)

Title: Dysphasia and Other Higher Cortical Dysfunctions During the Migraine Aura - a Systematic Review of Literature.

Authors: Igor Petrusic, Michele Viana, Chiara Zecca & Jasna Zidverc-Trajkovic.

Journal: Current Pain and Headache Reports (2020) 24:3 (M21)

Cilj ovog pregleda studija je bio da se utvrde svi simptomi koji ukazuju na više kortikalne poremećaje koji se javljaju tokom migrenske aure, kao i da se utvrdi njihova učestalost u napadima migrene sa aurom. Identifikovano je 5 studija koje su istraživale vrstu viših kortikalnih poremećaja tokom migrenske aure i prijavljene simptome od ukupno 697 pacijenata. Najčešći prijavljivani simptom viših kortikalnih poremećaja tokom aure pripadao je grupi disfazičnih poremećaja (10-53 %). Prisustvo vizuelnih viših kortikalnih poremećaja tokom aure je notirano kod 12-40 % pacijenata, somatosenzorni viši kortikalni poremećaji kod 12-20 % pacijenata, i poremećaji memorije kod 10-22 % pacijenata. Iako se migrena sa aurom karakteriše različitim simptomima viših kortikalnih poremećaja oni se nedovoljno istražuju i patofiziološki mehanizmi koji dovode do ovih poremećaja su nepoznati. Potrebna je bolja strategija za istraživanje viših kortikalnih poremećaja tokom aure kako bi se omogućila bolja fenotipizacija pacijenata i istraživanje patofizioločkih mehanizama koji dovode do migrenske aure.

3.2. Studija II – Karakteristike P3 ERP komponente kod podgrupa migrene sa aurom (Prilog II)

Title: P3 latency as a biomarker for the complexity of migraine with aura: Event-related potential study.

Authors: Igor Petrusic, Vojislav Jovanovic, Vanja Kovic & Andrej Savic.

Journal: Cephalalgia (2022) accepted (M21)

Cilj ove studije bio je da se uporedi P3 komponenta između osoba koje imaju migrenu sa aurom (MwA) i zdravih ispitanika, kao i da se uporede podgrupe pacijenata formirane u odnosu na kompleksnost napada MwA. Vizuelna "*oddball*" paradigma je korišćena kako bi se izazvali kognitivni potencijali (engl. *event-related potentials* - ERP). Amplitude i latencije P3 ERP komponente dobijene čestim i retkim stimulusima, kao i razlika dobijenih talasa čestih i retkih stimulusa za P3 ERP komponentu, su upoređivane između grupa i podgrupa. Prosečna vrednost MACS (*Migraine Aura Complexity Score*) je izračunata za svakog pacijenta kako bi se ispitala povezanost između karakteristika P3 ERP komponente i kompleksnosti aure. U studiji je učestvovalo 37 osoba koje imaju MwA (16 osoba koje imaju samo klasičnu vizuelnu auru – MwA-v i 21 osoba koja ima kompleksne aure – MwA-k) i 28 zdravih ispitanika. Kod osoba koje imaju MwA pokazano je da postoji značajno produženje P3 latencije u odnosu na zdrave ispitanike posmatrajući ERP snimljen tokom retkih stimulusa (411±39 ms vs. 372±34 ms, $p<0,001$). MwA-k podgrupa značajno se razlikovala od MwA-v podgrupe (427±34 ms vs. 389±35 ms, $p=0,004$) i zdravih ispitanika (372±34 ms, $p<0,001$) posmatrajući P3 latenciju dobijenu posle analize retkih stimulusa. Takođe, MwA-k podgrupa značajno se razlikovala od zdravih ispitanika (442±37 ms vs. 394±33 ms, $p<0,001$) posmatrajući P3 latenciju dobijenu kao razliku talasa dobijenih posle analize retkih i čestih stimulusa. Postoji pozitivna korelacija između P3 latencije koja je dobijana posle analize retkih stimulusa i MACS ($p<0,001$). Vizuelna "*oddball*" paradigma, posebno analiza retkih stimulusa, mogla bi poslužiti kao potencijalno novo sredstvo za precizno profilisanje osoba koje imaju različite kliničke manifestacije napada MwA. Takođe, dobijeni obrazac P3 ERP komponente predstavlja nove dokaze kognitivne disfunkcije kod osoba koje imaju MwA.

3.3. Studija III - Karakteristike N400 ERP komponente kod osoba koje imaju migrenu sa aurom (Prilog III)

Title: Characteristics of N400 component elicited in patients who have migraine with aura.

Authors: Igor Petrusic, Vojislav Jovanovic, Vanja Kovic & Andrej Savic.

Journal: The Journal of Headache and Pain (2021) 22:157 (M21a)

Cilj ove studije je bio da se istraži N400 efekat, kao i događajem izazvani kortikalni potencijali (engl. *event-related potentials* - ERP) dobijeni posle kongruentnih i nekongruentnih stimulusa, kod osoba koje imaju migrenu sa aurom (MwA). U studiju je uključeno 33 osobe koje imaju MwA i 20 zdravih ispitanika koji su upareni prema godinama starosti (35 ± 9 vs 35 ± 10 godina, p = 0,872) i prema polu (70 vs 75% ženski pol, p = 0,761). ERP-ovi su mereni kod obe vrste stimulusa (reč koja se prikazuje posle slike odgovara opisu slike – kongruentni stimulus i reč koja se prikazuje posle slike ne odgovara opisu slike – nekongruentni stimulus). Uprosečene vrednosti amplituda, pikova, latencija pikova, razlike u odgovorima kongruentnih i nekongruentnih stimulusa, i topografija upoređene su između osoba koje imaju MwA i zdravih ispitanika. Amplitude su značajno niže na Fz i F4 lokalizacijama, kao i pikovi na C3 i Pz lokalizacijama, kod osoba koje imaju MwA. Topografija je pokazala da je N400 efekat šire rasprostranjen preko skalpa glave nego kod zdravih ispitanika. Kombinovana analiza oba stimulasa pokazala je da postoji i P600 efekat koji je značajno slabije izražen kod osoba koje imaju MwA u odnosu na zdrave ispitanike na Pz (3.50 ± 3.15 vs 6.52 ± 2.57, p = 0.001) i P4 (3.95 ± 3.64 vs 5.86 ± 2.79, p = 0.040) lokalizacijama. Jačina N400 efekta se nije značajno razlikovala između grupa. Iz rezultata ove studije može da se zaključi da paradigma za izazivanje N400 efekta, koji se sastoji od procene da li reč koja se pojavljuje posle objekta sa slike tačno opisuje taj objekat ili ne, može da posluži kao potencijalni metod za proučavanje semantičkog procesiranja informacija kod osoba koje imaju MwA.

4. DISKUSIJA

U većini studija u kojima je fokus istraživanje migrene, osobe koje imaju MwA se ne odvajaju u posebnu grupu od osoba koje imaju isključivo migrenu bez aure iako je pokazano u nekoliko značajnih studija da su MwA i migrena bez aure dva različita entiteta koja delimično dele patofiziološke mehanizme u svojoj osnovi (Yilmaz i sar, 2001; Szabó i sar, 2018; Kincses i sar. 2019). Štaviše, studije koje su se fokusirale na istraživanje tipične MwA uglavnom nisu pravile razliku i nisu prijavljivali u rezultatima da li osobe pored vizuelnih simptoma imaju i nevizuelne simptome, kao što su somatosenzorni simptomi ili poremećaji viših kortikalnih funkcija (Eriksen i sar, 2004; Petrusic i sar, 2019a). Izostavljajući ove podatke u studijama onemogućeno je detaljnije analiziranje patofiziologije MwA i limitirane su mogućnosti za otkrivanje novih patofizioloških mehanizama i saznanja baziranih na dokazima koja bi vodila ka boljem individualnom tretmanu pacijenata koji boluju od tipične MwA u kojoj se javlja veliki spektar vizuelnih, somatozenzornih i ostalih poremećaja viših kortikalnih funkcija kao što su disfazija i poremećaj memorije u toku faze aure (Petrusic i sar, 2020).

Detaljnim pregledom literature, utvrđeno je da su simptomi više kortikalne disfunkcije prisutni kod osoba koje imaju tipičnu MwA u rasponu od 12-65 %, pri čemu su simptomi disfazije tokom aure prijavljeni kod 10-53 % pacijenata, a ostali simptomi viših kortikalnih poremećaja kod 10-40 % (Russell i Olesen, 1996; Eriksen i sar, 2004; Petrusic i sar, 2013; Petrusic i sar, 2014; Viana i sar, 2017). Učestalost ovih poremećaja je iznenađujuće visoka ukoliko se zna da postoji svega nekoliko studija koje su istraživale ove fenomene kod osoba koje imaju tipičnu MwA (Petrusic i sar, 2013; Petrusic i sar, 2014; Coppola i sar, 2021). Razlozi za mali broj studija koje istražuju razlike u podtipovima tipične MwA su pre svega što pacijenti ne prijavljuju ove simptome tokom rutinske anamneze i ne postoje standardizovani upitnici koji bi prikupili sve simptome koje osoba doživljava tokom napada MwA. Pažljivo prikupljanje simptoma koji nastaju zbog više kortikalne disfunkcije tokom aure omogućilo bi pravilnije opisivanje različitih fenotipova koji se javljaju kod MwA i dovelo bi do pravilnije stratifikacije pacijenata koji imaju MwA i formiranje homogenijih grupa u budućim studijama (Petrusic i sar, 2020; Petusic i Zidverc-Trajkovic, 2021).

U literaturi se simptom disfazije prijavljuje kao najčešći simptom višeg kortikalnog poremećaja tokom aure. Među najčešćim disfazičnim simptomima su parafazične greške, a zatim i disnomija i poremećaji u razumevanju tuđeg govora (Petrusic i sar, 2020). Važno je napomenuti da simptomi utrnulosti usta i jezika mogu dovesti do pogrešnog prijavljivanja disfazije, zbog čega je važno podpitanjima jasno diferencirati ove pojave od disfazičnih simptoma (Foroozan i Cutrer, 2009). Savremena tehnološka rešenja kao što je posebno dizajnirana mobilna aplikacija za prikupljanje podataka o karakteristikama aure mogla bi se koristiti u budućim prospektivnim studijama kao objektivan način za detektovanje disfazije tokom aure. Takođe, nova tehnološka rešenja mogu podstaći pacijente da postanu svesni svih simptoma tokom aure i da omoguće detaljnije profilisanje tipa MwA kod svakog pacijenta (Petrusic i sar, 2020).

Patofiziološki mehanizmi koji dovode do disfazičnih simptoma tokom aure nisu još uvek otkriveni. Poznato je da parafazične greške i poteškoće u pronalaženju reči mogu nastati zbog poremećaja funkcije neuromreže u angularnom girusu, Brokinoj regiji i srednjem temporalnom girusu (Chang, Raygor i Berger, 2015). Stoga, može se pretpostaviti da kod osoba koje imaju MwA različiti kortikalni regioni različito reaguju na talas kortikalne depolarizacije / depresije (Petrusic i sar, 2016), što dovodi do različitih kliničkih fenotipova disfazične aure. Takođe, pored poremećaja govora, tokom aure prijavljivane su i poteškoće u imenovanju poznatih lica i retrogradna amnezija što bi se moglo objasniti time da tokom širenja talasa kortikalne depolarizacije / depresije dolazi i do zahvatanjem fuziformnog girusa (Gainotti G i Marra, 2011; Petrusic i sar, 2013; Petusic i Zidverc-Trajkovic, 2014). Štaviše, poznato je da javljanje disfazičnih simptoma pozitivno korelira

sa dužim trajanjem aure što može dodatno osnažiti pretpostavku da talas kortikalne depolarizacije / depresije može dosegnuti do i zahvatiti fuziformni girus (Petusic i Zidverc-Trajkovic, 2014).

"Pozitivni" i "negativni" vizuelni i somatosenzorni simptomi koji nastaju usled poremećaj primarnih centara u vizuelnom i somatosenzornom korteksu su dobro opisane manifestacije MwA (Headache Classification Committee, 2018), dok su simptomi koji nastaju usled poremećaja viših kortikalnih centara u vizuelnom i somatosenzornom korteksu uglavnom nedovoljno prepoznati (Petrusic i sar, 2019a). Simptomi koji se javljaju usled poremećaja viših vizuelnih kortikalnih centara, kao što je poremećaj percepcije određenih boja, prijavljni su kod 11-20 % osoba koje imaju MwA što sugeriše da su različiti delovi okcipitalnog režnja uključeni u patofiziologiju migrenske aure (Petrusic i sar, 2013; Petrusic i sar, 2013; Viana i sar, 2017). Manualna dispraksija, definisana kao nemogućnost obavljanja manuelnih zadatka u odsustvu mišićne slabosti (Ochipa i Gonzalez-Rothi, 2000), predstavlja najčešći viši kortikalni poremećaj koji nastaje usled poremećaja funkcije viših kortikalnih centara u somatosenzornom korteksu (Petrusic i sar, 2020). Zašto neki pacijenti doživljavaju samo tipične somatosenzorne smetnje tokom aure, dok drugi imaju poremećaje viših somatosenzornih centara još uvek je nejasno. Jedno od mogućih objašnjenja jeste da varijabilan klinički fenotip MwA zavisi od individualnih urođenih predispozicaja ka podražljivosti određenih regija korteksa tokom širenja talasa kortikalna depolarizacije (Viana i sar, 2016). Svakako, klasifikacija pacijenata prema sličnom fenotipu aure omogućiće formiranje homogenijih podgrupa što će olakšati budućim studijama koje koriste neuroimidžing ili elektreofiziološke tehnike da otkriju patofiziološke mehanizme koji dovode do različitih manifestacija MwA (Petusic i Zidverc-Trajkovic, 2021). Jedan od bitnih koraka ka cilju bolje klasifikacije MwA jeste nedavno predloženi MACS - *Migraine Aura Complexity Score*, koji može olakšati diferencijaciju između kompleksnog napada MwA i napada koji nije kompleksan (Petrusic i sar, 2019a). Takođe, više zabeleženih napada MwA kod jednog pojedinca omogućiće određivanje prosečnog skora prema kome se može odrediti u koju podgrupu osoba treba da se svrsta.

Uprkos različitim rezultatima, većina studija je pokazala da osobe koje imaju MwA demonstriraju niže kognitivne performanse u odnosu na zdrave ispitanike (de Araújo i sar, 2012; Vuralli, Ayata i Bolay, 2018). Takođe, uprkos mnogim elektrofiziološkim studijama koje su proučavale osobe koje imaju MwA (Coppola i sar, 2019), nema dovoljno dokaza za karakterizaciju P3 ERP komponente. To je zato što većina objavljenih studija je istraživala vizuelne evocirane potencijale fokusirajući se na rane senzorne i perceptualne komponente u potrazi za elektrofiziološkim karakteristikama koji su u vezi sa MwA (Shibata, Osawa i Iwata, 1997; Coppola i sar, 2013). Pošto vizuelni evocirani potencijali obezbeđuju metod detekcije samo senzorne, ali ne i kognitivne obrade, oni se ne mogu porediti sa našim nalazima. Evers i njegove kolege, istražujući kognitivnu obradu informacija u primarnoj glavobolji, pokazali su da pacijenti koji boluju od MwA imaju povećanu amplitudu i dužu latenciju P3 ERP komponente u poređenju sa zdravim ispitanicima (Evers i sar, 1997). Štaviše, otkrili su da postoji poremećaj habituacije u vidu povećanja latencije P3 ERP komponente tokom više sesija snimanja ERP-a (Evers i sar, 1997). U našoj studiji, nismo pokazali značajne promene u amplitudi P3 ERP komponente, iako su pacijenti koji boluju od kompleksnih napada MwA imali trend ka povećanju P3-d amplituda (vrednost dobijena razlikom između P300 amplitude tokom retkih stimulusa – P3-r i P300 amplitude tokom čestih stimulusa – P3-č) u poređenju sa pacijentima koji boluju od migrene sa samo vizuelnom aurom i zdravim ispitanicima. Međutim, u prethodno pomenutoj studiji (Evers i sar, 1997), istraživači su uputili učesnike da pritisnu dugme kad god se pojavi crveno svetlo na ekranu (15 %) i da zanemare belo svetlo (85 %), što se razlikuje od naše paradigme i može uticati na poređenje sa našim rezultatima. Sa druge strane, naši rezultati su pokazali značajno povećanu latenciju P3-r kod pacijenata koji boluju od MwA, što je u skladu sa prethodnim rezultatima i može sugerisati produženje vremena kognitivnog procesiranja informacija kod osoba koje imaju MwA kada se

suočavaju sa retkim stimulansima (Patel i Azzam, 2005; Huang i sar, 2017). Ovo je dalje potvrđeno produženim vremenom reakcije za oba (česte i retke) stimulusa kod osoba koje boluju od MwA, što je u skladu sa prethodnim nalazima (Evers i sar, 1997).

Štaviše, naši nalazi podržavaju teoriju o različitim nivoima složenosti patofizioloških mehanizama kod podtipova MwA (Petrusic i sar, 2019a; Coppola i sar, 2021). Zapravo, naša studija predstavlja prve rezultate vizuelno izazvane P3 ERP komponente kod osoba sa detaljnim podacima o karakteristikama njihove MwA, uključujući i kompleksnost aure, što nam omogućava da istražimo povezanost između kompleksnosti aure i kognitivne obrade informacija u interiktalnoj fazi (Petrusic i sar, 2022). U našoj studiji rezultati ukazuju da je produžena latencija P3-r kod osoba koje imaju kompleksniju auru u odnosu na zdrave ispitanike i osobe koje imaju samo vizuelne simptome tokom aure, kao i da je produžena latencija P3-d u poređenju sa zdravim ispitanicima (Petrusic i sar, 2022). Štaviše, MACS pozitivno korelira sa P3-r latencijom, sugerišući da P3-r latencija može biti obećavajući elektrofiziološki biomarker za procenu kompleksnosti MwA i pouzdan metod za dalje istraživanje osnova višeslojne patofiziologije MwA.

Prema našem saznanju, ispitivanje N400 efekta kod osoba koje imaju MwA do sada nije sprovedeno, iako je poznato da pacijenti koji imaju MwA tokom napada često prijavljuju simptome disfazije (Petrusic i sar, 2019a). U ovoj studiji koristili smo dva eksperimentalna uslova, reči koje se poklapaju ili ne poklapaju sa prikazanim slikama, da bismo proučavali semantičke procese obrade informacije zasnovane na N400 efektu kod pacijenata koji imaju MwA. Analiza ERP-a je pokazala da su amplitude N400 komponente za nekongruentne stimuluse niže kod osoba koje imaju MwA u odnosu na zdrave ispitanike (Petrusic i sar, 2021). Ovaj rezultat može ukazati na slabije formiranje postsinaptičkih potencijala i/ili na manju vremensku sinhronizaciju među ekscitiranim neuronima koji utiču na N400 ERP komponentu tokom nekongruentnih stimulusa (Kutas i Federmeier, 2011). Svakako, kombinovanje ERP studija sa funkcionalnim tehnikama neuroimidžinga može otkriti pravi uzrok ovih razlika.

N400 efekat nije se značajno razlikovao između ispitivanih grupa. Izostanak interakcije između N400 efekta i grupa je očekivan jer se poremećaj N400 efekta javlja samo u teškim oblicima mentalnih bolesti kao što je shizofrenija (Jackson i sar, 2014). N400 efekat, u vremenskom prozoru između 260 i 460 milisekundi posle pojave reči koja opisuje objekat sa slike, pokazao je karakterističnu centralno-parijetalnu prostornu distribuciju kod zdravih ispitanika što je u skladu sa prethodnim studijama sprovedenim na zdravim populacijama (Šoškić i sar, 2021). U MwA grupi postoji dodatna distribucija N400 efekta prema frontalnim regionima. U kontekstu ovog istraživanja, dobijene morfološke i topografske razlike mogu se pripisati složenoj disregulaciji senzorne obrade informacija kod osoba koje imaju MwA.

Važno je napomenuti da je analizom ERP-a uočen talas koji je dostigao pik oko 550-600 milisekundi i da je bio niže amplitude u MwA grupi. Takozvana P600 ERP komponenta može ukazati na dodatni proces praćenja semantičke integracije, odražavajući procenu da li je podudaranje slike i reči bilo prikladno ili ne (Savic, Savic i Kovic, 2017). Ovi rezultati, zajedno sa nižom amplitudom N400 ERP komponente, mogli bi da ukazuju da pacijenti koji imaju MwA demonstriraju povećane zahteve za semantičkom obradom informacija (Kutas i Federmeier, 2011). Ukoliko se u budućim studijama utvrdi da je bilo koji od ovih faktora u vezi sa promenama u ERP-ovima izazvanim iz N400 paradigme, onda bi N400 i P600 ERP komponente mogle da posluže u svakodnevnoj praksu u centrima za migrene kao dodatna mera za praćenje statusa pacijenata, u pogledu promene učestalosti simptoma i njihove kompleksnosti, ili za praćenje odgovora na određeni tretman. Prednost predloženog eksperimentalnog protokola je zato što se brzo sprovodi (prosečno trajanje oko 5 minuta po osobi).

5. ZAKLJUČCI

Na osnovu dobijenih rezultata mogu se izvesti sledeći zaključci:

1) Pregledom literature je utvrđeno da je simptom disfazije najprevalentniji simptom koji ukazuje na poremećaj viših kortikalnih funkcija tokom faze aure i da je takođe najspecifičniji simptom koji ukazuje na kompleksnu migrensku auru. U nedostatku jasnih kriterijuma za distinkciju između kompleksne i ne-kompleksne aure, pojava simptoma disfazije tokom aure može poslužiti kao kriterijum za određivanje podtipa tipične migrenske aure.

2) MACS (eng. Migraine Aura complexity Score – skor za procenu kompleksnosti aure) može sveobuhvatno da proceni kompleksnost aure i može da se preporuči za buduće studije koje imaju za cilj da istraže patofiziološke razlike između podtipova tipične migrene sa aurom ili da procene uticaj terapije na tok bolesti.

3) Osobe koje boluju od migrene sa aurom imaju suptilnu kognitivnu disfunkciju tokom interiktalne faze, koja se ogleda u značajno dužoj latenciji P3 ERP komponente u odnosu na zdrave ispitanike posmatrajući ERP snimljen tokom retkih stimulusa.

4) Vizuelna "*oddball*" paradigma, posebno analiza retkih stimulusa, mogla bi da posluži kao potencijalno novo sredstvo za precizno profilisanje osoba koje imaju različite kliničke manifestacije napada migrene sa aurom. Štaviše, produžena latencija P3 ERP komponente tokom retkih stimulusa može da posluži kao potencijalni biomarker za kompleksne napade migrene sa aurom ili kao odgovarajući korelat kompleksnosti aure i procenjenom MACS-u.

5) Paradigma za izazivanje N400 efekta, koji se sastoji od kongruentnog i nekongruentnog stimulusa, može da posluži kao potencijalni metod za proučavanje semantičkog procesiranja informacija kod osoba koje imaju MwA.

6) Paradigma za izazivanje N400 efekta, posebno analiza nekongruentnog stimulusa, mogla bi da posluži kao potencijalno novo sredstvo za otkrivanje disfunkcije kognitivnog i semantičkog procesiranja informacija tokom interiktalne faze kod osoba koje imaju migrenu sa aurom.

7) Na osnovu svih rezultata ispitivanja obuhvaćenih ovom tezom, može da se zaključi da je potrebna bolja karakterizacija kliničkih i elektrofizioloških fenotipova migrene sa aurom kako bi se omogućilo otkrivanje novih načina terapije različitih podtipova bolesti i utvrdile smernice za individualniji pristup terapije kod pacijenata koji boluju od migrene sa aurom.

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7. PRILOZI

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Dysphasia and Other Higher Cortical Dysfunctions During the Migraine Aura—a Systematic Review of Literature

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Abstract

Purpose of the Review Although visual and somatosensory disturbances are the most common migraine aura (MA) symptoms, patients can also experience other symptoms during their MA. The aim of this review is to provide an overview of studies that report symptoms of dysphasia and other higher cortical dysfunctions (HCDs) during MA, as well as to determine the frequency of HCDs.

Recent Findings Five studies met the inclusion criteria, corresponding to 697 patients overall. The most frequently reported HCDs were those of the language group (range 10–53%). The occurrence of visual HCDs was noted in 12–40 patients, somatosensory HCDs in 12–20%, and memory disturbances in 10–22% of the patients during MAs.

Summary MA is associated with a wide range of neurological symptoms, including symptoms of HCD. A better strategy for investigation of the HCD symptoms is needed to correctly stratify patients thus allowing meaningful studies of aura pathophysiology.

Keywords Migraine with typical aura · Dysphasia · Higher cortical dysfunctions · Disturbances of visual perception · Somatosensory disturbances

Introduction

Migraine is the second most disabling disorder in the world [1], with 30% of patients having migraine with aura [2]. This transient event consists of the onset of neurological symptoms with a gradual development that precedes or accompanies the headache [3]. The most frequent migraine aura (MA) symptoms are visual and somatosensory disturbances [3]. MA can also include other symptoms, i.e., higher cortical dysfunctions (HCDs) [4••]. HCDs are disturbances derived from dysfunctions of polymodal associative cortical areas that integrate sensory information of different modalities [4••]. They can belong to visual (e.g., micropsia, macropsia, dysmorphia, fractured vision, and prosopagnosia), somatosensory (e.g., astereognosis, dyspraxia, and neglect of own body parts), language (e.g., Broca's dysphasia, Wernicke's dysphasia, and dysnomia), and memory groups (e.g., difficulties in remembering or recalling events or names, and calculating and/or memorizing numbers). Among these, the language group is probably the most common and studied one [4••, 5, 6•, 7•, 8, 9, 10•].

Cortical spreading depression (CSD) is a widely accepted model that explains the pathogenesis of migraine aura [11–13]. However, it is not well understood whether CSDs start always in the same area (i.e., occipital—V1), spread always in a given direction, are unifocal and/or multifocal, as well as if these can also originate in silent auras [10•, 14]. In spite of major progress in neuroimaging opportunities, results of neuroimaging studies are conflicting, and mechanisms that allow manifestations of HCD symptoms during the typical

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aura remain largely unknown [15–18]. Careful investigation of these symptoms and their functional imaging correlates are therefore needed in this field.

At present, no literature exists on the frequency of HCDs during MA. Identifying all HCD symptoms that could be a part of the typical aura attack and their frequency could shed a light on new pieces of the puzzle of MA pathophysiology, which can lead to more individualized therapy for migraineur patients. Our aim was to provide an overview of the published data about the frequency of occurrence of the different HCD symptoms during typical MAs.

Methods

Literature Search

We performed a systematic literature search identifying articles reporting on HCDs during typical MAs with information on how frequently different HCDs are reported by MA patients. The literature search was performed on 19 April 2019. We used PubMed/MEDLINE combining the key words "migraine aura" with the words "dysphasic," "dysphasia," "aphasia," "paraphasic errors," "dysnomia," "dyslexia," "color-naming disorder," "higher cortical," "higher cognitive," "prosopagnosia," "visual dysgnosia," "change of colors," "astereognosis," "deformed images," "retrograde amnesia," "deja vu," "auditory dysgnosia," "neglect of own body parts," "dyspraxia," "dysgraphia," "dyscalculia," and "memory disturbances." Articles from the reference list of studies that were found to be relevant, known to be relevant by the authors or reported within the references of ICHD-3 were also considered.

Data Extraction

Three authors independently reviewed the abstracts found in the literature search (IP, MV, JZT). If the title or abstract indicated relevant data (investigation of MA features), the entire manuscript was examined. Those original articles that described HCDs and their frequencies were eligible for further analysis. The quality assessment of the included studies was done by applying the NIH Quality Assessment Tool for observational cohort and cross-sectional studies. We did not consider articles that only reported a prevalence of dysphasia without further data about the quality of speech disturbances or other HCDs. Also, we excluded case studies and review articles. Only articles in English were considered. Inclusion and exclusion criteria were based on an expert consensus between the authors. The following data were collected from relevant papers: publication information (authors and year), included subjects (number of patients, gender distribution, and mean age), study methodology (type of population, study design, and methods of data acquisition), and aura features (frequency of aura symptoms, aura duration, frequency of HCD, and frequency of each HCD's symptoms). Data extraction was conducted independently by 2 members (IP and MV) of the research team to reduce or eliminate errors in the data compiled for analysis.

Results

The search strategy identified 237 studies. Of these, $N = 27$ were found to be relevant, and 5 fulfilled the inclusion/exclusion criteria [4••, 6•, 7•, 8, 10•], yielding a total of 697 patients evaluated about the HCD symptoms during the aura. Of note, the studies by Vincent and Hadjikhani [5], Manzoni et al. [19], Russell et al. [20], Alstadhaug et al. [21], Hansen et al. [22], Petrusic et al. [23••], and two studies by Queiroz [24, 25] were excluded as it was not possible to correctly estimate the frequency of HCDs due to the study design.

Out of the five selected studies, two were specifically designed to identify the presence of HCDs during MA [4••, 6•] whereas three studies reported the types and frequency of some HCDs among other MA disturbances [7•, 8, 10•]. All studies have moderate risk of bias because the data were collected between attacks and HCDs were determined based on patients' reports.

The most frequently reported HCD symptoms were those of the language group (which occurred in $N = 214/697$ patients) (Table 1). Paraphasic errors were the most predominant symptoms among the patients who reported dysphasia (Table 2). Visual HCD had a frequency of occurrence ranging from 1 to 40%. The most frequent symptoms were dyschromatopsia and deformed images (reported respectively in 13–20% and 11% of patients), followed by prosopagnosia, macropsia, micropsia, and alteration of distance perception (respectively 2–3%, 2%, 2%, and 1% of cases). Data about somatosensory and memory HCDs were shown in two papers [4••, 6•]. They occurred in patients with a frequency ranging respectively from 12 to 20% and from 15 to 22%. The most common symptoms in each group were respectively dyspraxia and the deja vu phenomenon.

There was a positive correlation between aura duration and the number of HCDs [4••].

Discussion

MA can manifest with visual and somatosensory disturbances, and sometimes also with one or more HCD symptoms, which could be a disabling experience. The majority of studies has focused on typical MA symptoms and have neglected to report HCD symptoms with the exception of language HCD [8].

Table 1 Summary of studies that investigated the frequency and types of higher cortical dysfunctions (HCD) during migraine aura among patients. Symptoms of HCD are expressed as *N* (%) of patients with respect to all the patients in the study population.

Authors	Subjects			Auras Number	Methodology			Results					
	Number of patients	Age mean ± SD (years)	Gender (F:M)		Type of population	Design	Data acquisition methods	Aura symptom prevalence	HCD** *N* (%)	V-HCD** *N* (%)	S-HCD** *N* (%)	L-HCD** *N* (%)	M-HCD** *N* (%)
Russell and Olesen (1996) [7•]*	163	45 ± 16	68:95	163	MA patients, all aged 40 years old, selected with a questionnaire from the general population	Retrospective study	Direct or telephone interview with a physician	VA in 99% pts, SA in 31% pts, AA in 18% pts, and MA in 6% pts	n/a	n/a	n/a	29 (18)	n/a
Eriksen et al. (2004) [8]*	362	46 ± 16	263:99	362	MA patients with familial occurrence selected from the general population	Retrospective study	Patients were asked to describe the most common aura theywere able to recall.	VA in 98% pts, SA in 54% pts, and AA in 32% pts	n/a	n/a	n/a	116 (32)	n/a
Petrusic et al. (2013) [4••]	60	39 ± 13	44:16	n/a	MA patients selected from a clinical database	Retrospective study	Direct interview with a physician (physician asked questions from a questionnaire that was specially designed to investigate types of HCDs during migraine aura).	VA in 97% pts, SA in 57% pts, and AA in 53% pts	39 (65)	8 (13)	7 (12)	32 (53)	9 (15)
Petrusic et al. (2014) [6•]	40	16 ± 2	20:20	n/a	MA patients selected from a clinical database	Retrospective study	Direct interview with a physician (physician asked questions from a questionnaire that was specially designed to investigate types and frequencies of HCDs during migraine aura).	VA in 100% pts, SA in 60% pts, and AA in 37% pts	22 (55)	16 (40)	8 (20)	15 (37)	9 (22)
Viana et al. (2017) [10•]	72	41 ± 14	58:14	216	Consecutive MA patients from a tertiary referral headache center	Prospective study	Diary entries during the aura phase (patient was asked to describe each aura symptom (visual, sensory and dysphasic) in his/her own words (in the diary, there was a free-text box for each symptom))	VA in 98% pts, SA in 36% pts, and AA in 10% pts	n/a	9 (12)	n/a	22 (10)	n/a

F:M, female to male ratio; *MA*, migraine aura; *VA*, visual aura; *SA*, somatosensory aura; *AA*, aphasic aura; *MTA*, motor aura; *HCD*, higher cortical dysfunction; *V-HCD*, visual HCD; *S-HCD*, somatosensory HCD; *L-HCD*, language HCD; *M-HCD*, memory-HCD

*A few HCDs were specifically inquired

**The number of patients with at least one symptom of the whole group

Table 2 Type and frequency (*N*/TOT(%)) of different HCDs among patients in the five studies found in literature

	Russell (1996) [7•]	Eriksen (2004) [8]	Petrusic (2013) [4••]	Petrusic (2014) [6•]	Viana (2017) [10•]
Language group					
Paraphasic errors *N* (%)	22/163 (13)	96/362 (27)	n/a	11/40 (27)	3/72 (4)*
Dysphasia nominum *N* (%)	21/163 (13)	n/a	12/60 (20)	3/40 (7)	4/72 (5)*
Receptive dysphasia *N* (%)	11/163 (3)	26/362 (7)	n/a	2/40 (5)	n/a
Dyslexia *N* (%)	n/a	n/a	8/60 (13)	10/40 (25)	n/a
Visual group					
Dyschromatopsia *N* (%)			8/60 (13)	8/40 (20)	n/a
Deformed images *N* (%)			n/a	n/a	8/72 (11)
Prosopagnosia *N* (%)			2/60 (3)	1/40 (2)	n/a
Macropsia *N* (%)			1/60 (2)	n/a	n/a
Micropsia *N* (%)			1/60 (2)	n/a	n/a
Alteration of distance perception *N* (%)			n/a	n/a	1/72 (1)
Somatosensory group					
Manual dyspraxia *N* (%)			7/60 (12)	8/40 (20)	n/a
Neglecting hand symptom *N* (%)			n/a	2/40 (5)	4/72 (5)§
Astereognosis *N* (%)			1/60 (2)	2/40 (5)	n/a
Memory group					
Retrograde amnesia *N* (%)			2/60 (3)	4/40 (10)	
Anterograde amnesia *N* (%)			9/60 (15)	2/40 (5)	
Deja vu phenomenon *N* (%)			8/60 (13)	9/40 (22)	

*These symptoms were spontaneously reported by patients; the authors did not ask specifically about every subtype of language disturbance

§These symptoms were spontaneously reported by patients in a textbox where patients were allowed to report other symptoms (non-visual/somatosensory/dysphasic), unpublished data

According to our review, HCD symptoms have a frequency of occurrence overall ranging from 12 to 65%, with dysphasic symptoms and non-dysphasic HCDs ranging from 10 to 53% and 10–40%, respectively [4••, 6•, 7•, 8, 10•]. This frequency is surprisingly high, considering the few published studies which investigated them [4••, 6•]. Reasons for this underreporting may include their lower recognizability by patients as compared with visual or somatosensory disturbances, and the difficulty of screening for their presence either by history taking or questionnaires. A careful collection of HCD symptoms in MA would enrich the already multifaceted scenario of MA phenotypes [8] and enable a better stratification of the MA patients to identify more homogeneous groups for further investigations.

According to our systematic research, dysphasic aura was the most frequently reported of the HCD symptoms, paraphasic errors being the most common manifestation followed by symptoms of dysnomia and receptive dysphasia. It should be noted that cheiro-oral sensory changes may lead to speech difficulties as well, which should not be misdiagnosed with dysphasic aura [26]. Similarly, difficulty with speech, and difficulties with reading or writing are respectively reported among premonitory symptoms in 9% and 20% of the 803 prospectively recorded attacks [27], representing a further confounding source. Modern technology solutions such as a specially designed mobile application for collecting data about MA features during or after the MA attack could be used in future prospective studies to explore objective measures that help to distinguish language impairment during premonitory and aura phases. These technology solutions can also encourage patients to be aware of these symptoms.

Paraphasic errors and word-finding difficulties could be linked to the angular gyrus, Broca's region, or middle temporal gyrus [28]. Therefore, among migraineurs different cortical regions react differently to CSD and associated factors [29], leading to various clinical phenotypes of the dysphasic aura. In addition to speech disturbances, difficulties in naming familiar persons and recalling information from the past were also reported during MAs. Despite not being supported by

functional imaging studies yet, the impact on the medial temporal gyrus and/or inferior parietal lobule by CSD could mutually influence memory and speech processes, thus accounting for language and memory alterations [30, 31]. Moreover, since it has been shown that the number of HCDs correlate with aura duration, the influence of aura duration on the occurrence of dysphasia and memory disturbances should be further investigated [4••].

While positive or negative visual and somatosensory symptoms are well-described manifestations of MA, HCD of visual and somatosensory cortical regions still remain underrecognized. Our goal was to investigate their types and frequency of occurrence; however, we found few papers [4••, 6•] investigating this topic. Visual HCDs were notable in those studies involving 11 to 20% of migraineurs with aura [4••, 6•, 10•]. Change of perceived colors was the most commonly reported visual HCD [4••, 6•]. It has to be underlined that these studies did not take into consideration the potential influence of photophobia, which can be misinterpreted as the colors becoming brighter. Future studies with appropriate design are needed to address this issue. Various types of visual disturbances suggest different involvement of the occipital lobe by CSD [32], which remains to be investigated.

Manual dyspraxia, defined as the inability to perform a task in the absence of weakness, incoordination, or movement disorders, represents the most frequent somatosensory HCD [33]. The site responsible for dyspraxia is probably not unique, as many parietal-temporal-frontal networking systems are required for movement planning [34]. However, why some patients experience elementary somatosensory disturbances during their MA, while others have somatosensory HCD remains unclear. One possible explanation is that the variable clinical phenotype depends on different thresholds at which underlying pathophysiological processes translate into symptoms among patients [9].

Also, it should be stressed that one of the relevant studies [6•] investigated HCDs only in the teenage population. However, the findings of this study did not differ from studies that investigated frequencies of HCDs in the adult population suffering from MA. It was only noticeable that dyslexia, dyschromatopsia, and manual dyspraxia were slightly more prevalent in the teenage population. The relevance of these findings, because of a relatively small sample size, cannot be duly discussed.

State-of-the-art neuroimaging of the nervous system is one of the most useful approaches for investigating aura subtypes. Although neuroradiological studies of MA have become more and more appreciated in recent years [35–43], there is still inadequate accent on the investigation of inter-individual structural and functional brain changes in patients with MA. According to our knowledge, there are only four papers that investigated the differences between MA patients who experience HCD during the aura and those without HCD [15, 44•, 45, 46]. Compared with MA patients without HCD, those with HCD demonstrated a significantly reduced cortical surface area and volume of the left rostral middle frontal cortex [44•]; have more myelinated fibers in the right inferior longitudinal fasciculus, forceps minor, right superior longitudinal fasciculus (parietal and temporal parts), and cingulum-angular bundle [45]; and exhibit a thicker cerebral cortex in the left and right hemispheres overall and in some of their regions, among which the left and right lateral occipital, right cuneus, right precuneus, left postcentral, and left and right superior parietal cortices were the most significant [46]. These specific structural findings may either be associated with an increased propensity to experience disturbances of higher cortical functions during MA or be the consequence of this clinical phenotype. Confirmatory studies as well as new data analysis of brain activation, connectivity, network level of cortical processes, and structure in migraine with aura are warranted to clarify this point [47].

Importantly, the studies considered within this review carry many limitations. Firstly, most of the data were retrospectively collected, therefore exposing them to recall biases. Secondly, the classification into different HCD phenotypes was based on patients' reports without any specific neuropsychological assessments. Thirdly, in some studies, patients were inquired about the presence of each subtype of HCD with specific questions [4••, 6•], whereas in other cases, some HCDs were spontaneously reported [7•, 8, 10•]. Moreover, the number of patients included in these studies is rather small and ranges from 40 to 362. Also, patients were selected from tertiary headache centers, making it impossible to extrapolate the prevalence of HCDs in the whole population of patients with MA. These flaws could be overcome with prospective studies which include neuropsychological assessments to correctly classify different HCD types. Correct classification of patients according to the similar aura phenotype will contribute to future neuroimaging, neurophysiological, and genetic studies.

Conclusions

Migraine aura is associated with a wide range of HCD symptoms, which have been poorly investigated until now. A precise dissection of the HCD phenotypes is a fundamental step for the design of meaningful studies investigating the underlying pathophysiological mechanisms. Moreover, if certain HCDs prove to occur more frequently during the aura, a case could be made for modifying the current diagnostic criteria and classification. Future studies should address this issue because identifying subtypes of typical MA might lead to more individualized therapy of migraineurs patients.

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Compliance with Ethical Standards

Conflict of Interests The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: IP, MV, MD, and JTZ have no conflict of interest.

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7.2. Studija II

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P3 latency as a biomarker for the complexity of migraine with aura: Event-related potential study

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Abstract

Background: This study aimed to compare the P3 component between patients who have migraines with aura and healthy subjects, and to compare different subtypes of migraine with aura relative to the complexity of migraine aura.
Methods: Average Migraine Aura Complexity Score was calculated for each MwA patient. Visual oddball paradigm was used to elicit the P3 component. P3 amplitudes and latencies elicited from frequent and rare stimuli, as well as from difference wave, were compared with healthy subjects. Subsequently, subtypes of migraine with aura were compared and Average Migraine Aura Complexity Score was used to explore the connection between features of the P3 and complexity of migraine with aura.
Results: 37 patients who have migraine with aura (16 with simple aura and 21 with complex aura) patients and 28 healthy subjects were studied. Patients who have migraine with aura had significantly prolonged latencies compared to healthy subjects (411 ± 39 ms vs 372 ± 34 ms, $p < 0.001$) relative to a rare condition. Patients who have complex aura significantly differs from patients who have simple aura (427 ± 34 ms vs 389 ± 35 ms, $p = 0.004$) and healthy subjects (372 ± 34 ms, $p < 0.001$) relative to P3 latency in a rare condition and the patients who have complex aura significantly differs from healthy subjects (442 ± 37 ms vs 394 ± 33 ms, $p < 0.001$) relative to P3 latency in difference wave. P3 latency from rare condition positively correlated with the Average Migraine Aura Complexity Score ($p < 0.001$).
Conclusions: Visual oddball paradigm, particularly rare stimuli, could serve as a potential new tool for deep profiling of different clinical complexities among patients who have migraine with aura. Also, the present pattern of P3 components provided new evidence for the cognitive dysfunctions in patients who have migraine with aura.

Keywords

Electroencephalography, headache, cognitive processing, oddball paradigm, dysphasia

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Introduction

Event-related potential (ERP) is a reliable and non-invasive neurophysiological examination that can reflect underlying brain activities during cognitive processing and has been increasingly employed as a cognitive biomarker in various neurological diseases (1,2). P3, the most investigated ERP component, is considered an effective index of cerebral information processing during a cognitive task (3). In the literature, there are no consistent differences of P3 characteristics in ERP evoked by an oddball paradigm between patients who have migraine, other headache types, and healthy subjects (HSs) (4–6). Several ERP studies

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have assessed the cognitive function in migraine patients and showed reduced P3 amplitudes (6,7), while there was also evidence that the P3 component was enlarged and delayed in migraine patients (8,9). Moreover, P3 amplitude was significantly reduced during mind wandering relative to on-task periods in migraine patients, which is in contrast to what was observed in HSs (10). All these opposite findings could be because researchers in previous studies recruited patients with different stages of the migraine cycle or different migraine phenotypes (migraine without aura (MwoA) and migraine with aura (MwA) or even different MwA subtypes) in different proportions in a single group (11). Also, an important finding in P3 studies is the lack of habituation during an interictal phase in patients who have a migraine, where results showed an acceleration of the P3 latency during the second trial (5,9).

It is well known that some MwA patients report abundant symptomatology of higher cortical disturbances during MwA attacks (12,13). Moreover, it is suggested that MwA patients could suffer from subtle cognitive changes during the interictal period (14,15). The most frequently reported cognitive changes were impaired visual and verbal memory, reduced information processing speed, executive dysfunction and attention deficit (11,16). The presence of cognitive impairment in MwA patients reinforces the complexity of this disease, which is not exclusively associated with pain symptoms (11). In fact, recent studies also suggest different layers of MwA pathophysiology among MwA subtypes (17–20). Moreover, a migraine aura complexity score (MACS) has been proposed in a recent study which could serve for quantification of the complexity of MwA attack (21). Knowing that MwA attacks could differ from one attack to another in the same person, it is suggested to use MACSs to calculate average MACS for the evaluation of mean MwA complexity in one patient and consequently help with the stratification of MwA patients into subgroups relative to theirs MwA complexity (22).

P3 studies conducted on a homogenous group of patients who have typical migraine aura are scarce and there is no comparison between MwA subgroups in terms of migraine aura complexity by using an oddball paradigm and recording ERP. Considering the aforementioned, the present study aimed to compare the P3 component between MwA patients and HSs, as well as to compare the P3 component between MwA patients who have only visual symptoms and those who have visual and somatosensory or dysphasic aura. Also, we aimed to correlate features of the P3 component with the estimated complexity of migraine aura.

Methods

This is an observational, descriptive, cross-sectional and quantitative study, which was approved by the Scientific Ethics Committee of Clinical Center of Serbia and Neurology Clinic (reference number: 23-690). All standards and guidelines of the World Medical Association Declaration of Helsinki were respected. The participants signed a written informed consent form before participation.

Participants

Patients who had episodic typical MwA (23) were recruited between 2019 and 2020 from the migraine population referring to the Center for headaches, Neurology Clinic, Clinical Center of Serbia. Patients with neurological (other than MwA), psychiatric, cardiovascular and metabolic disorders were excluded because they did not fit the profile chosen for the study. The minimum age for participating in this study was 21 years. Also, all MwA patients did not take any migraine preventive medications at the time of the enrolment in the study. Additionally, 28 HSs, balanced with MwA by age, sex and education, and with no family history of migraine were recruited. HSs were voluntarily recruited from clinical staff or their relatives and friends, who upon acceptance underwent physical and neurological examinations. Also, all participants underwent an MRI examination to exclude intracranial lesions.

Clinical data, such as MwA attack frequency, the average disease duration and migraine aura symptoms, were obtained via patient's diary and structured electronic questionnaire which patients regularly filled after every MwA attack. From the electronic records, the last six consecutive MwA attacks before the ERP recording were used to calculate the average MACS for each patient. The range of MACS is 0–9, with higher values indicating a more complex aura (21). Average MACS was used in the study to correlate MwA complexity with the P3 component derived from an oddball paradigm. Because the MACS are still undergoing validation process, we decided to stratify MwA patients into a subgroup of patients who have simple MwA (only visual symptoms during the aura – MwA-s) and those who have complex MwA (visual symptoms plus somatosensory and dysphasic symptoms during the aura – MwA-c), which is more recognizable from the point of the International Headache Society terminology (23).

ERP study design and processing of signals

All MwA patients were both migraine-free and not taking any medications at least three days before or

after ERP recordings. Every MwA patient and HS received instructions before electrophysiological recordings started. Then, they were seated in a chair with a monitor placed 60 cm in front of them. To ensure the instructions were understood and followed correctly, short subject training was performed.

Each trial started with a fixation cross in the center of the screen with a jittered time range between 300 and 700 milliseconds (ms) that varied from trial to trial. Next, the letter O (frequent stimulus; 0.8 probability of occurrence) or X (rare stimulus; 0.2 probability of occurrence) appeared, which remained on the screen for three seconds or until response. Participants were instructed to press the left mouse button for the frequent stimulus and the right mouse button for the rare stimulus. Letters appeared in black Mono 24 px font against a light gray background. There were 300 trials in total including 240 trials for frequent condition and 60 trials for rare condition. For stimuli presentation, we used OpenSesame 3.3.9 (24).

Electroencephalography (EEG) signals were recorded continuously from the scalp in monopolar setup from 35 electrode sites positioned according to the international 10/20 standard: Fp1, Fp2, F7, F8, FT9, FT10, T7, T8, F3, Fz, F4, FC5, FC6, FC1, FC2, FCz, C3, Cz, C4, CP5, CP6, CP1, CP2, P3, Pz, P4, TP9, TP10, P7, P8, PO9, PO10, O1, Oz, and O2. All electrodes were referenced to the left earlobe, and the ground electrode was positioned at the AFz location. Skin-electrode contact impedance levels were maintained below 5 kO. EEG was recorded with a sampling rate of 1000 Hz.

Offline signal processing was conducted using custom MATLAB code (Version 2015a, The Mathworks, Natick, MA, USA). EEG channels were band-pass filtered using a zero-phase 4th order Butterworth filter in a range of 0.1–25 Hz. Individual 1000-ms EEG epochs (from –100 to 900 ms), with 0 marking the stimulus, including 100 ms pre-stimulus baseline and 900 ms post-stimulus data, were extracted from the continuous filtered EEG. All EEG channels were baseline corrected by subtracting the mean amplitude of the baseline from each epoch. The trials were inspected for artifacts (eye movement, blinks, high amplitude drifts). Only the noise-free trials associated with correct subjects' responses were included in further analyses. Data from 1 MwA patient was rejected due to the presence of noise which resulted in a high number of rejected epochs per experimental condition (>30). For each participant and each condition at each electrode site, individual ERPs were calculated by averaging all remaining trials. Additionally, the difference ERP waveforms were calculated for each subject by subtracting the average ERPs (of each channel) of the frequent condition from the averaged ERPs of the rare condition. The positive peak between 300–500 ms was used to define the P3 component. Amplitudes and latencies for the P3 component were extracted from waves elicited by frequent stimuli (P3-f) and rare stimuli (P3-r), as well as from the difference wave (P3-d).

Statistical analyses

For the analyses of demographic and clinical variables among groups, we used descriptive statistics (mean ± standard deviation and percentage), parametric test (the Independent Student T-test for age and education) and nonparametric test (the Chi-square test for sex). Also, parametric and nonparametric tests were used for the analysis of behavioral data. $P < 0.05$ was considered statistically significant.

The effect of the oddball paradigm was assessed with an analysis of variance with grouping factors of participant status (MwA vs HSs), experimental factors (frequent vs rare stimuli) and recording site. The recording site included two dimensions: anterior-posterior distribution and laterality. The anterior-posterior dimension grouped frontal (F3, Fz, F4), central (C3, Cz, C4), and parietal (P3, Pz, P4) electrodes. The laterality dimension grouped left (F3, C3, T3), middle (Fz, Cz, Pz), and right (F4, C4, P4) electrodes. The amplitudes and latencies of P3-f and P3-r were used for repeated analysis of variance (ANOVA) In the case of significant interactions, they were broken down following subsequent analysis in an attempt to understand the locus of the interaction. A Greenhouse-Geisser correction was used in cases of sphericity violation. Significant main effects were further explored by follow-up t-tests. For the analysis of amplitudes between groups and subgroups, we used the Mann-Whitney U test, while the Independent Student T-test was used for the analysis of latency differences. Pearson and Spearman correlation coefficients were used to examine connections between clinical, behavioral and ERP data.

Results

Clinical and demographic data

A total of 37 MwA (16 MwA-s and 21 MwA-c) patients and 28 HSs were studied. They were balanced in age (37 ± 9 years vs 36 ± 9 years, $p > 0.9$), sex (70% females vs 71% females, $p = 1.0$) and education (15 ± 2 years vs 15 ± 3 years, $p > 0.9$). MwA attack frequency per year was 7 ± 8 attacks. The average disease duration was 19 ± 10 years. The mean of average MACS of all MwA patients included in this study was 3 ± 2 points.

MwA-s did not differ significantly from MwA-c in age (37 ± 9 years vs 36 ± 9 years, $p = 0.8$), sex (62%

females vs 77% females, $p = 0.5$), education (15 ± 2 years vs 15 ± 2 years, $p = 0.7$), attack frequency (4 ± 2 attacks vs 9 ± 10 attacks, $p = 0.2$) and average disease duration (19 ± 9 years vs 18 ± 12 years, $p = 0.9$). The mean of average MACS significantly differs between subgroups as expected (0.9 ± 0.7 points vs 4.6 ± 1.8 points, $p < 0.001$).

Behavioral data

There was a significant difference between MwA and HSs in the reaction time for frequent (330 ± 97 ms vs 265 ± 62 ms, $p = 0.002$) and rare (415 ± 79 ms vs 360 ± 63 ms, $p = 0.003$) stimuli. There was no significant difference between MwA and HSs in the number of errors for frequent (0.2 ± 0.6 errors vs 0.2 ± 0.4 errors, $p = 0.9$) and rare (3.0 ± 2.8 errors vs 3.2 ± 2.6 errors, $p = 0.6$) stimuli during the task.

Subsequently, MwA-s and MwA-c subgroups were compared to the HSs group. MwA-c significantly differs from the HSs group relative to the reaction time for frequent ($p = 0.009$) and rare ($p = 0.029$) stimuli, while MwA-s did not differ from the HSs group ($p = 0.1$ and $p = 0.051$, respectively). There was no significant MwA-subgroup difference in the reaction time for frequent (318 ± 97 ms vs 339 ± 99 ms, $p = 0.5$) and rare (414 ± 80 ms vs 415 ± 80 ms, $p > 0.9$) stimuli. Also, the number of errors during the task did not differ between MwA-s and MwA-c subgroups for frequent (0.1 ± 0.2 errors vs 0.3 ± 0.7 errors, $p = 0.4$) and rare (2.4 ± 2.0 errors vs 3.4 ± 3.2 errors, $p = 0.5$) stimuli.

ERP data

The grand averaged ERP curves of both experimental conditions, including difference wave, for all participants at the frontal (F3, Fz, F4), central (C3, Cz, C4) and posterior (P3, Pz, P4) regions are shown in Figure 1. Regarding the analysis of P3 amplitudes, repeated measures ANOVA showed the main effect of condition ($p < 0.001$), with higher amplitudes in a rare condition. There was no significant interaction between effect and groups ($p = 0.3$).

Regarding the analysis of P3 latencies, repeated measures ANOVA showed the main effect of condition ($p < 0.001$), with longer latencies in rare condition. An effect × region × lateralization interaction was also detected ($p < 0.001$), as well as effect × group ($p < 0.001$), effect × region ($p < 0.001$) and effect × lateralization ($p < 0.001$) interactions. Subsequent analysis at the Pz site revealed that the MwA group had significantly longer latencies compared to HSs (411 ± 39 ms vs 372 ± 34 ms, $p < 0.001$) relative to a rare condition, while P3 latencies in frequent condition did not differ between groups (344 ± 31 ms vs 345 ± 48 ms, $p > 0.9$). Further analysis of subgroups showed

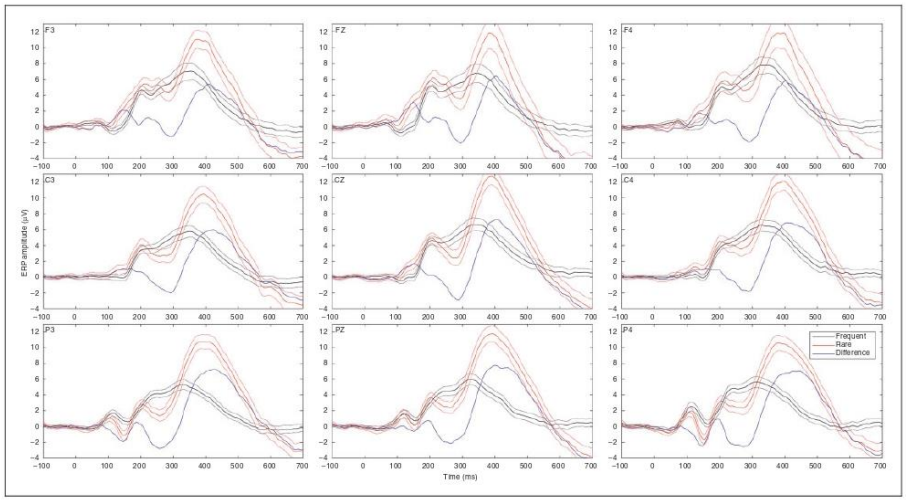

Figure 1. The grand averaged ERP curves of frequent (black line) and rare condition (red line) with confidence intervals (dotted lines) were presented at the frontal, central and posterior channels. The blue line represents the difference wave which reveals the P3 effect.

Table 1. Amplitudes and latencies derived from the Pz channel for the frequent and rare conditions and difference wave in the MwA-c, MwA-s and HSs.

	MwA-c (n = 21)	MwA-s (n = 16)	HSs (n = 28)	Statistics*
P3-f amplitude (μV)	6 ± 3	7 ± 3	8 ± 3	$p = 0.2$
P3-f latency (ms)	345 ± 36	343 ± 26	345 ± 48	$p > 0.9$
P3-r amplitude (μV)	15 ± 5	14 ± 5	16 ± 4	$p = 0.4$
P3-r latency (ms)	427 ± 34	389 ± 35	372 ± 34	**$p < 0.001$** (MwA-c vs MwA-s, $p = 0.004$; MwA-c vs HSs, $p < 0.001$)
P3-d amplitude (μV)	12 ± 5	11 ± 4	12 ± 4	$p = 0.6$
P3-d latency (ms)	442 ± 37	418 ± 38	394 ± 33	**$p < 0.001$** (MwA-c vs HSs, $p < 0.001$)

HSs: healthy subjects; MwA-c: patients who have migraine with complex aura; MwA-s: patients who have migraine with simple aura; ms: milliseconds; μV: microvolts; P3-d: P3 component derived from difference wave; P3-f: P3 component derived from frequent stimuli; P3-r: P3 component derived from rare stimuli. *ANOVA was used for all 3 groups analysis and T-test with Bonferroni correction for post hoc analysis if needed.

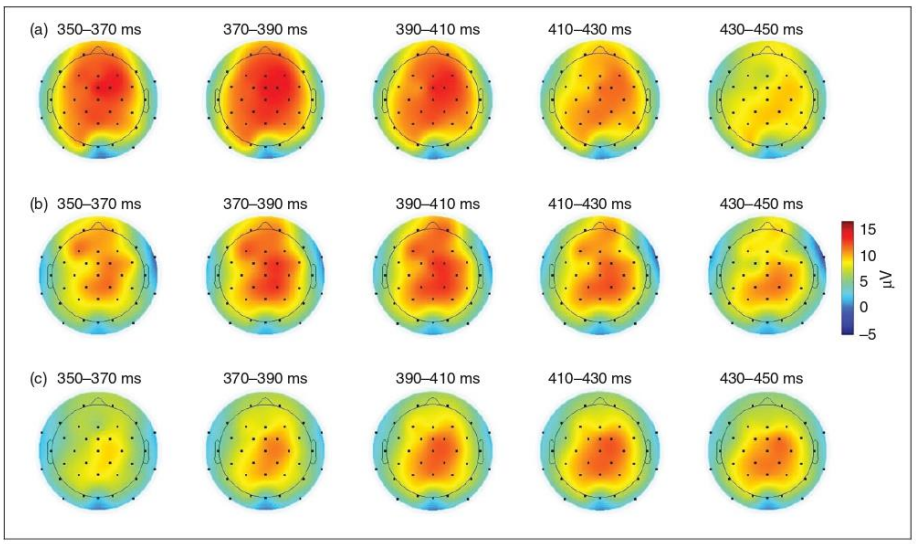

Figure 2. EEG topography derived from the grand averaged ERPs elicited by rare task stimuli in HSs (a), MwA-s (b) and MwA-c (c). Topographic maps show mean ERP amplitude in five 20-ms windows in a range of 350–450 ms. The gradual delay of the P3 peak is observed in MwA-s compared to HS and MwA-c compared to MwA-s and HS. Topographic maps show also a trend of wider distribution and higher P3 peak in HSs compared to MwA-s and MwA-c subgroups.

that the MwA-c subgroup significantly differs from MwA-s and HSs at the Pz site with regards to P3 latency in a rare condition and the MwA-c subgroup significantly differs from HSs with regards to P3 latency in difference wave (Table 1, Figure 2 and Figure 3).

Further, clinical and behavioral data of MwA patients were correlated with P3 latency derived from frequent and rare conditions from the Pz site. There was a positive correlation between time response for frequent stimuli and P3-f latency (Pearson correlation coefficient = 0.6, $p < 0.001$), as well as between time response for rare stimuli and P3-r latency (Pearson correlation coefficient = 0.4, $p = 0.023$). Also, there was a positive correlation between MACS and P3-r latency (Spearman correlation coefficient = 0.6, $p < 0.001$). There was no significant correlation between the MACS and P3-f latency (Spearman correlation coefficient = 0.05, $p = 0.8$). MwA attack frequency and the average disease duration did not correlate significantly with P3-f and P3-r latencies.

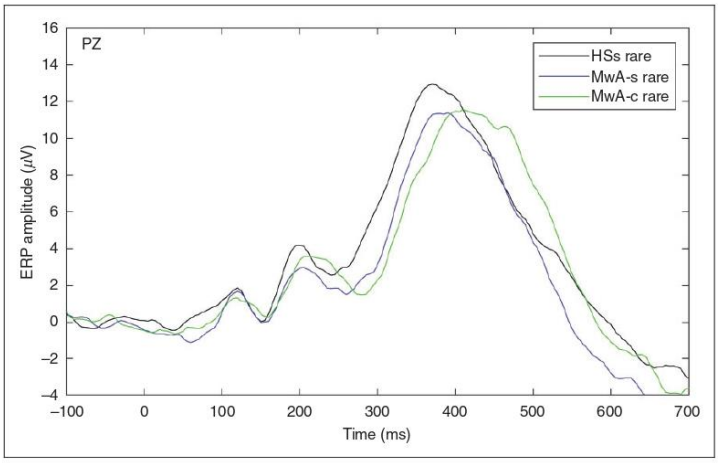

Figure 3. The grand averaged ERP curves of HSs (black line), MwA-s (blue line) and MwA-C (green line) groups derived from the rare stimuli at the Pz site.

Discussion

Despite mixed results, most studies found that MwA patients have lower cognitive performance than HSs (11). Our results resonate with this observation. Moreover, our findings support the theory of different levels of complexity of disease in MwA patients (22,25). This is, in fact, the first study of visually evoked P3 component in the largest number of carefully clinically studied patients who have typical MwA allowing us to investigate the influence of aura complexity on interictal cognitive processing in MwA patients. In the present study, the latency of the P3-r was prolonged in MwA compared to HSs group and MwA-c subgroup had prolonged P3-r and P3-d relative to HSs and P3-r compared to MwA-s subgroup.

Neurophysiological tools, such as the P3 component, have shown promising usefulness as an indicator of certain impairments of cognitive processes (11). The P3 component in many ERP studies is obtained using the so-called oddball paradigm, in which a sequence of standard (non-target) stimuli is randomly interrupted by infrequent target stimuli (26). This kind of paradigm elicits the P3 component, located at the centro-parietal region, which seems to correlate with attention, information processing and executive functions (27). Also, there is a hypothesis that the P3 may result from the operation of neural inhibition caused by brain mechanisms intending to inhibit extraneous brain activation when cognitive processes are engaged by stimulus and task demands (2,28). Furthermore, since rare stimuli can be biologically important, it is adaptive to inhibit unrelated activity to promote processing efficiency thereby yielding large P3 amplitudes (2). Regardless of these numerous functions of the P3 component, it is widely accepted that P3 latency reflects the length of stimulus evaluation processes when a two-choice reaction time is required (29) and its amplitude is largely determined by the amount of attention allocated to the stimulus (30).

Despite many electrophysiological studies of MwA (25), there is no sufficient evidence to characterize the P3 component in MwA patients. This is because most previous studies did not analyze MwA patients separately from MwoA patients. Furthermore, most of the published studies investigated visual evoked potentials focusing on early sensory and perceptual components to search for brain signatures associated with MwA (31,32). Since those visual evoked potentials provide a method of detecting only sensory but not cognitive processing, they cannot be compared to our findings. Evers et al. (9), investigating cognitive processing in primary headache, showed that MwA patients had increased P3 amplitude and longer latency compared to healthy controls. Moreover, they found an acceleration of the P3 latency during the second trial, which indicated a loss of cognitive habituation in MwA patients (9). We did not demonstrate significant changes in the P3 amplitude, although MwA patients

had a trend towards decreased P3-f and P3-r amplitudes, as well for P3-d with exception of MwA-c patients, who had trends toward increased P3-d amplitude compared to MwA-s patients and HSs. However, in the previously mentioned study (9), investigators instructed participants to press a button whenever the red light occurred on the screen (15%) and to ignore the white light (85%), which is different from our paradigm and can influence comparison to our results. On the other hand, our results showed significantly increased P3-r latency in MwA patients, which is in line with the previous results and can suggest the prolongation of the cognitive processing time in MwA patients when facing rare stimuli (1,33). This is further confirmed with prolonged reaction time for both (frequent and rare) stimuli in MwA patients, which is in line with previous findings (9).

There were significant correlations between reaction time for frequent stimuli and P3-f latency and reaction time for rare stimuli and P3-r latency, which is expected because reaction time is influenced by cognitive processes and evaluation of the stimuli, as well as by selection processes and activation or execution of the motor response (34). Our behavioral data analysis revealed significant differences between MwA-c and HS groups for reaction times to both frequent and rare stimuli. However, P3 latencies differed significantly between the MwA-c and HS only for rare but not for frequent stimuli. This reveals group differences in cognitive processing of stimulus type (frequency), reflected in P3-r latency, but not reaction time measures. Thus, our behavioral findings could suggest impaired activation and execution of the motor response in MwA patients in general, but prolonged P3-r and P3-d latencies point out cognitive dysfunction during stimulus evaluation. Moreover, reaction time did not differ between MwA subgroups, while P3-r latency was significantly prolonged in the MwA-c relative to the MwA-s subgroup, suggesting more impaired cognitive dysfunction during stimulus evaluation in the MwA-c subgroup. This reveals that P3-r and P3-d latencies induced within the visual oddball task are sensitive measures for characterizing migraine complexity unlike behavioral outcome measures in our study which further confirms its biomarker potential.

To our knowledge, an ERP study focusing on the P3 component, that investigates subgroups of MwA patients has never been done. Thus, we are first to report that P3-r and P3-d latencies are prolonged in MwA-c patients compared to MwA-s patients and HSs. Moreover, the MACS positively correlated with the P3-r latency, suggesting P3-r latency as a promising electrophysiological biomarker for evaluation of the MwA complexity and reliable tool for further investigation of underpinnings of multilayered MwA pathophysiology. It is also worth noting that MwA-c and MwA-s groups did not differ in age, since ERPs are age-dependent (35). Altogether, these results suggest subtle abnormalities in attentional processing in MwA patients, particularly linked to the complexity of MwA attacks, and indicate that further studies should focus on understanding the impact of MwA on everyday life in patients during the interictal period (36). Also, knowing that MwA patients frequently experience interictal cognitive difficulties such as heightened sensitivity to extraneous sensory inputs (37,38), supported by the results which point to an increase in grand-average neural response to any kind of sensory stimuli due to deficient short-term and long-term adaptive processes to external stimuli (10), prolonged latency of P3 component, in the light of inhibitory theory, may suggest abnormalities in the compensatory strategy for reducing stimulus overload in the cortex (10). If this hypothesis is valid, this explanation can elucidate the positive correlation between P3 latency and MwA complexity. This can be further strengthened by the result that stratification of MwA patients according to the distinctive manifestations in typical aura pointed to the same finding, which challenges the point of view that patients who have only visual symptoms and someone who has visual and somatosensory or dysphasic aura should be equally weighted and placed in the same group, as already discussed in the previous neuroimaging study (22). Furthermore, the frequency of MwA attacks and disease duration did not seem to influence cognitive performance and ERP parameters, which is also found in other studies of migraine with aura (9,39).

In closing, we would like to restate the procedural decisions that can somewhat constrain the interpretation of the present findings. First, this study is limited by the lack of comparison with MwoA patients, thus our results could not be interpreted as specific for MwA patients. Second, the inclusion of fMRI findings would significantly improve the interpretation of our results, which we hope will be a future step for confirming our ERP study. Third, we did not investigate the habituation of latencies in MwA patients due to the lower number of rare stimuli used to evoke the P3 component. Our study aimed to explore the potential of the P3 component as a clinically applicable biomarker of the MwA and its complexity. We, therefore, aimed to apply a simple and fast protocol of visual oddball paradigm with an optimized number of stimuli per experimental condition. The strength of the study is that MwA patients were carefully divided into homogenous groups according to their clinical phenotypes and they did not have any comorbidity, nor did they take

prophylactic treatment, such as Topiramate, which could influence the study results (40). Finally, the results of this study should be confirmed using a new and independent cohort of subjects.

Conclusion

P3 component of ERP as a response to rare stimuli within the visual oddball paradigm is a promising tool for investigation of cognitive processes in patients who are affected by numerous and varied clinical MwA features and can help in more deep profiling of different clinical complexities among MwA patients. Overall, the present pattern of P3 components provided new evidence for the dysfunction of cognitive function in MwA patients. Finally, we strongly believe that a better characterization of clinical and electrophysiological phenotypes of MwA will lead to novel, individually oriented and tailored therapeutic interventions.

Clinical implications

- The P3 component could serve as an auxiliary biomarker in distinguishing patients who have complex aura symptoms from those who have simple visual auras.
- The visual oddball paradigm, particularly rare stimuli, could be a promising tool for further investigation of cognitive processes in brains who are affected by numerous and varied clinical features of migraine with aura.
- Combined characterization of clinical and electrophysiological phenotypes of MwA patients could point to novel and individually oriented therapeutic treatment.

Author Contributions Statement

IP contributed to the study aim, design, acquisition, analysis, interpretation and drafting of the manuscript. VJ contributed to the acquisition, analysis and interpretation of data. VK contributed to the study design, interpretation and revising of the manuscript. AS contributed to the study aim, design, analysis, interpretation, revising of the manuscript and supervision. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Medical Ethics Committee of the Neurology Clinic, Clinical Center of Serbia, and was conducted following the Declaration of Helsinki. Informed consent forms were completed by all the participants after receiving an explanation of the study.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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7.3. Studija III

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RESEARCH ARTICLE Open Access

Characteristics of N400 component elicited in patients who have migraine with aura

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Abstract

Background: This study aimed to examine the N400 effect and event-related potentials (ERPs) elicited from congruent and incongruent stimuli in patients who have migraines with aura (MwA).

Methods: A total of 33 MwA patients and 20 healthy controls (HCs) were studied. They were balanced in age (35.12 ± 8.94 vs 34.70 ± 9.59 years, $p = 0.872$) and sex (69.7 vs 75.0% females, $p = 0.761$). ERPs were measured in response to both stimuli, where pictures were preceded with an object name that either matched or mismatched with the object. Averaged amplitudes, peaks, peak latencies, difference waves and topography were compared between MwA and HCs.

Results: MwA patients had significantly lower averaged amplitudes at the Fz and F4 sites during incongruent stimuli, as well as reduced peaks at the C3 and Pz sites. Topography showed a more widespread N400 effect over scalp relative to HCs. The difference ERP waveforms did not differ in the N400 effect between groups, but the P600 effect was significantly stronger in the HCs group relative to the MwA group at the Pz (6.52 ± 2.57 vs. 3.50 ± 3.15, $p = 0.001$) and P4 (5.86 ± 2.79 vs. 3.95 ± 3.64, $p = 0.040$) sites.

Conclusions: Picture-word matching tasks could serve as a potential new method for the investigation of semantic processing in MwA patients.

Keywords: Electroencephalography, Event-related potentials, Headache, Semantic processing, Source localization

Introduction

Migraine with aura (MwA) is a worldwide highly prevalent disorder that can have a tremendous impact on everyday life [1, 2]. Although it is well known that during MwA attack cognitive dysfunction is present in various forms, recent studies also suggest that MwA patients could suffer from subtle cognitive changes during the interictal period [3–6]. Furthermore, it is known that cortical spreading depression, which is a pathophysiological substrate of migraine aura, could disrupt cortical function and also could be a cumulative risk factor for cerebrovascular events [7].

All of the above support the importance of investigating the cortical dysfunction outside of MwA attack as a relevant target for further better understanding of complex and multilayered MwA pathophysiology. Moreover, given that dysphasia is a common symptom during MwA attack [8] and that MwA patients also can have subtle impairment of verbal functioning interictally [9, 10], new approaches to the investigation of interictal verbal functioning and cognitive function in MwA patients are needed.

One of the interesting ways to investigate subtle semantic differences changes is an N400 component of the event-related potential (ERP) measured by electroencephalography (EEG) [11]. N400 component could be observed in lexical priming paradigms, where a target word was or was not somehow related to an immediately preceding (prime) word or picture. Compared to a

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congruent condition where words and object referents are presented correctly with one another, words and pictures that are not matching elicit an ERP component that has a more negative amplitude, peaking around 300–500 milliseconds (ms) after the onset of the word, with a most visible effect on centro-parietal electrodes [12]. An advantage of this technique is that it provides an immediate and continuous record of the neural processes associated with evaluating a cognitive stimulus with a high temporal resolution, allowing to directly and precisely measure when different computational processes underlying semantic memory are taking place in the brain [11, 13].

There are no papers, to our knowledge, that explored brain activation in a picture-word priming paradigm using event-related potentials during an interictal period in MwA patients. This study aims to correct this lack by studying ERP parameters in a group of patients who have episodic migraines with typical aura and to compare them with healthy controls (HCs). Since ERPs are already recognized as promising biomarkers which can provide sensitive, objective and reliable measures of the neural events underlying cognition in neurological disorders [14], this study aims to pave the way for exploring their potential role as biomarkers in migraine. Moreover, ERPs-based biomarkers could be able to identify different MwA phenotypes or serve as a measure of the response to specific treatment [15].

Methods

Participants

Thirty-five patients with exclusively episodic typical MwA, according to the International Headache Society criteria [16], were recruited between 2019 and 2020 from the migraine population referring to the Center for headaches, Neurology Clinic, Clinical Center of Serbia. Patients were without neurological (other than MwA), psychiatric, cardiovascular and metabolic disorders. All patients were both migraine-free and not taking any medications at least 3 days before electrophysiological recordings of a brain during a cognitive task. Also, all patients did not take any migraine preventive medications at the time of the study. Additionally, twenty-three age- and sex-balanced HCs with no family history of migraine or other neurological and other chronic systemic diseases were recruited. HCs were voluntarily recruited from clinical staff or their relatives and friends, who upon acceptance underwent physical and neurological examinations. Also, MRI was performed to exclude intracranial lesions in all participants.

The study was approved by the Scientific Ethics Committee of Clinical Center of Serbia and Neurology Clinic (reference number: 23–690). The study conforms with the World Medical Association Declaration of Helsinki. The subjects signed a written informed consent form before participation.

ERP study design and processing of signals

Participants were asked to sit in a comfortable chair in an electrically shielded room and to observe a 17-in CRT monitor that was placed 60 cm in front of them. Each trial started with a fixation cross in the center of the screen for the jittered time range between 300 and 700 ms that varied from trial to trial. Next, the image appeared for 700 ms, immediately followed by the target word which remained on the screen for three seconds or until response (Fig. 1). Participants were instructed to press the left mouse button click for the picture-word match (congruent stimulus) and the right mouse button for the picture-word mismatch (incongruent stimulus). Words appeared in black Mono 24 px font against a light gray background. There were in total 120 trials including 60 trials for match condition and 60 trials for mismatch condition. For stimuli presentation, we used OpenSesame 3.3.9 [17].

Stimuli were obtained by using image databases Photodisc collection and Hemera Photo-Objects, as well as internet Google Image Search. Sixty pictures of easily nameable and recognizable objects, such as animals, everyday objects, fruits, etc. were selected. All stimuli were cropped and resized to fit a box of approximately 300 × 300 pixels, presented on a light gray background in the middle of the screen (to prevent eye movements during the task). Each image was paired with a target word (noun), which was related (name of the picture) or unrelated to the presented picture, making two picture-word sets (match vs. mismatch condition).

EEG signals were recorded continuously from the scalp in monopolar setup from 35 electrode sites positioned according to the international 10/20 standard: Fp1, Fp2, F7, F8, FT9, FT10, T7, T8, F3, Fz, F4, FC5, FC6, FC1, FC2, FCz, C3, Cz, C4, CP5, CP6, CP1, CP2, P3, Pz, P4, TP9, TP10, P7, P8, PO9, PO10, O1, Oz, and O2. All electrodes were referenced to the left earlobe reference, and the ground electrode was positioned at the AFz location. Skin-electrode contact impedance levels were maintained below 5 kO. EEG was recorded with a sampling rate of 1000 Hz.

Offline signal processing was conducted using custom MATLAB routines (version 2015a, The Mathworks, Natick, MA, U.S.A.). All EEG channels were band-pass filtered using a zero-phase 4th order Butterworth filter with 0.1–25 Hz cut-off frequencies. Individual 1000 ms EEG epochs, with 0 marking the stimulus, which included 100 ms pre-stimulus baseline and 900 ms post-stimulus data, were extracted from the continuous filtered EEG. All EEG channels were baseline corrected by subtracting the mean amplitude of the 100 ms

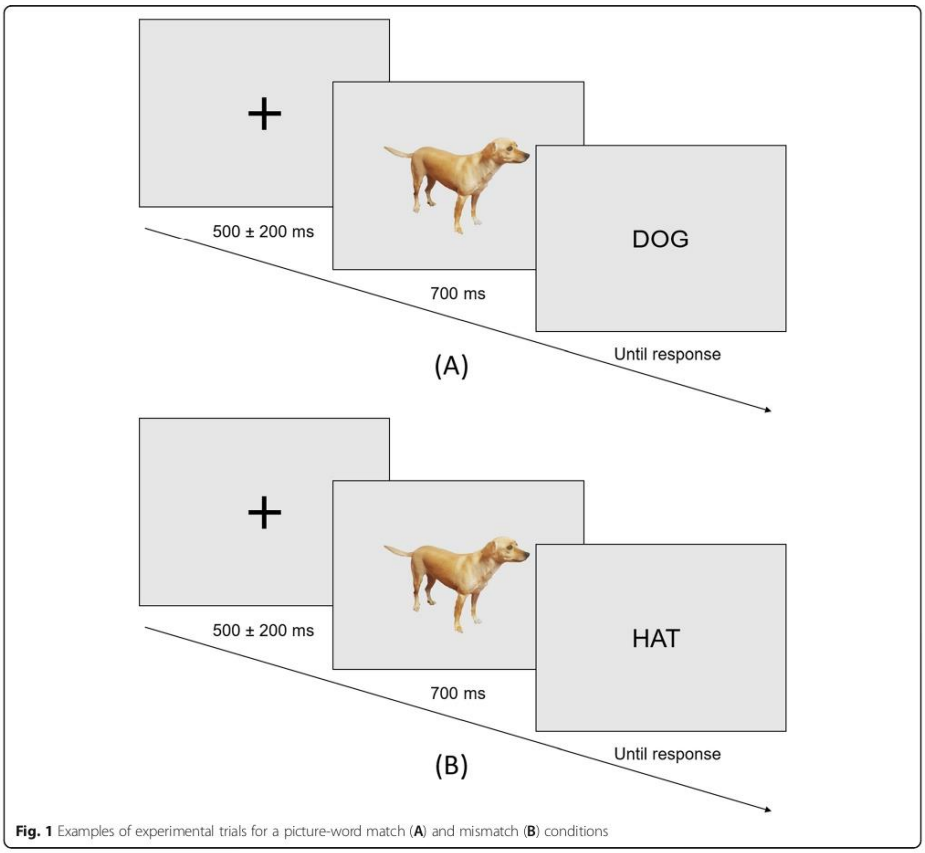

Fig. 1 Examples of experimental trials for a picture-word match (**A**) and mismatch (**B**) conditions

baseline from each epoch. The trials were inspected for artifacts and only the noise-free trials were included in further analyses. Data from 2 MwA patients and 3 HCs were rejected due to the presence of noise which resulted in a high number of rejected epochs per experimental condition (> 30). For each participant and each condition at each electrode site, individual ERPs were calculated by averaging all remaining trials. Additionally, the difference ERP waveforms were calculated for each subject by subtracting the average ERPs (of each channel) of the incongruent condition from the averaged ERPs of congruent condition.

Average ERPs and difference waves for each channel were segmented into 20 ms non-overlapping time bins and mean amplitude for each time bin was calculated.

Statistical analyses

For the analyses of demographic and clinical variables among groups, we used descriptive statistics (mean ± standard deviation and percentage), parametric test (the Independent Student T-test for age) and nonparametric test (the Chi-square test for sex). $P < 0.05$ was considered statistically significant.

Effects of MwA on priming were assessed with an analysis of variance with grouping factors of participant status (MwA vs. HCs), experimental condition (congruent vs. incongruent stimuli) and recording site. The recording site included two dimensions: anterior-posterior distribution and laterality. The anterior-posterior dimension grouped frontal (F3, Fz, F4), central (C3, Cz, C4), and parietal (P3, Pz, P4) electrodes. The

laterality dimension grouped left (F3, C3, T3), middle (Fz, Cz, Pz), and right (F4, C4, P4) electrodes. The average amplitude value of the selected window (260–460 ms) for the determined N400 component was used for mixed model repeated ANCOVA which was corrected for sex and age of participants. We applied mean amplitude measurement that calculates the mean voltage of the waveform in a predetermined window of time because this method is advised when investigated cognitive processes do not occur at fixed latencies over trials or subjects [18]. In the case of significant interactions, they were broken down following subsequent analysis in an attempt to understand the locus of the interaction. Significant main effects were further explored by follow-up t-tests. A Greenhouse-Geisser correction was used in cases of sphericity violation. The *p*-value for significance testing was 0.05. For the analysis of amplitudes between groups, we used the Mann-Whitney U test, while the Independent Student T-test was used for the analysis of latency differences. The false discovery rate (FDR) correction for multiple comparisons was applied. Also, statistical analysis of peaks and latencies was conducted for a selected window at all pre-selected channels.

Furthermore, for deeper exploratory analysis, we aimed to identify for each of the selected subsets of 9 EEG channels electrodes around a vertex (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4) the time instants corresponding to statistically significant differences between groups. The Mann-Whitney U test and Independent t-test were used for this purpose.

Results

A total of 33 MwA patients and 20 HCs were studied. They were balanced in age (35.12 ± 8.94 vs 34.70 ± 9.59 years, $p = 0.872$) and sex (69.7 vs 75.0% females, $p = 0.761$). The average disease duration was 17.81 ± 11.02 years. MwA attack frequency per year was 6.00 ± 6.55.

The grand averaged ERP curves of both experimental conditions, including difference wave, for all participants at the frontal (F3, Fz, F4), central (C3, Cz, C4) and posterior (P3, Pz, P4) regions are shown in Fig. 2. The window (260–460 ms) that shows the N400 effect was used

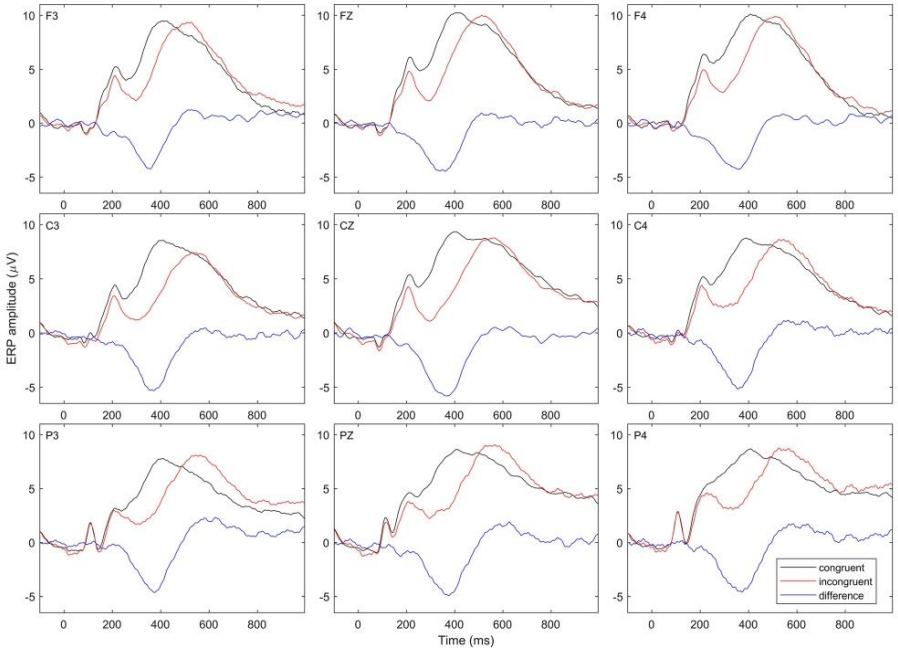

Fig. 2 The grand averaged ERP curves of congruent (black line) and incongruent condition (red line) were presented at the frontal, central and posterior channels. The blue line represents the difference wave which reveals the N400 effect

for the calculation of averaged amplitude value for each participant and repeated ANCOVA was conducted. Mixed model repeated measures ANCOVA showed the main effect of experimental condition ($p < 0.001$), with lower amplitudes in mismatch condition (incongruent stimuli). The main effect of the region was also detected ($p = 0.037$), with lower amplitudes on central and posterior electrodes compared to the frontal set ($p < 0.001$). There was no significant interaction between effect and groups ($p = 0.200$). A region x laterality x group interaction was also detected ($p = 0.028$), as well as region x group interaction ($p = 0.007$). The age ($p = 0.538$) and sex ($p = 0.331$) of participants did not influence significance of the results. Because of the complex scalp distribution effects, follow-up tests were conducted at each of the preselected sites to examine detected interactions.

Comparison between groups relative to the experimental condition, N400 component and electrode sites revealed that during incongruent stimuli MwA patients had significantly lower amplitudes at the Fz and F4 sites (Table 1). Also, incongruent stimuli pointed to the difference between groups at the C3, Cz, C4 and Pz sites, but statistical significance did not persist after the FDR correction. The peak of the N400 component during the incongruent stimuli was significantly lower in MwA patients relative to HCs at the C3 and Pz sites. Moreover, incongruent stimuli pointed to the difference between groups at the Fz, F4, Cz, C4, P3 and P4 sites, but statistical significance did not persist after the FDR correction. The peak latency of the N400 component during the incongruent stimuli was reduced in MwA patients relative to HCs at the Pz and P4 sites.

Table 1 Amplitudes and latencies derived from 9 pre-selected channels for the congruent and incongruent conditions in MwA and HCs

		Congruent condition			Incongruent condition		
		MwA (*n* = 33)	**HCs (*n* = 20)**	**Statistics**	**MwA (*n* = 33)**	**HCs (*n* = 20)**	**Statistics**
F3	Averaged N400 (μV)	6.20 ± 3.55	9.50 ± 6.47	$p = 0.095$	3.51 ± 3.94	7.13 ± 6.55	$p = 0.072$
	Peak (μV)	10.85 ± 5.70	15.01 ± 9.65	$p = 0.132$	8.65 ± 5.21	13.18 ± 9.97	$p = 0.095$
	Latency (ms)	380 ± 60	389 ± 49	$p = 0.600$	396 ± 71	393 ± 70	$p = 0.876$
Fz	Averaged N400 (μV)	6.61 ± 4.28	10.88 ± 7.37	$p = 0.099$	2.95 ± 4.39	8.28 ± 6.31	**$p = 0.004$***
	Peak (μV)	10.89 ± 5.43	16.82 ± 10.46	$p = 0.056$	8.01 ± 5.16	14.57 ± 9.35	**$p = 0.010$**
	Latency (ms)	383 ± 62	387 ± 59	$p = 0.818$	397 ± 72	422 ± 51	$p = 0.145$
F4	Averaged N400 (μV)	7.10 ± 3.58	10.52 ± 6.94	$p = 0.110$	3.55 ± 3.79	8.20 ± 6.14	**$p = 0.004$***
	Peak (μV)	10.96 ± 5.19	16.30 ± 10.50	$p = 0.078$	8.27 ± 4.94	14.28 ± 10.27	**$p = 0.024$**
	Latency (ms)	383 ± 58	393 ± 58	$p = 0.576$	407 ± 74	419 ± 54	$p = 0.538$
C3	Averaged N400 (μV)	5.67 ± 3.21	8.23 ± 4.90	$p = 0.085$	1.55 ± 3.59	4.88 ± 4.20	**$p = 0.009$**
	Peak (μV)	9.42 ± 4.03	12.60 ± 6.91	$p = 0.097$	5.44 ± 4.23	9.93 ± 6.35	**$p = 0.004$***
	Latency (ms)	392 ± 52	388 ± 50	$p = 0.751$	404 ± 70	402 ± 72	$p = 0.915$
Cz	Averaged N400 (μV)	6.46 ± 3.66	9.49 ± 5.64	**$p = 0.036$**	1.82 ± 4.22	5.17 ± 4.74	**$p = 0.024$**
	Peak (μV)	10.25 ± 4.16	14.16 ± 7.45	$p = 0.072$	5.98 ± 4.90	10.53 ± 6.60	**$p = 0.009$**
	Latency (ms)	388 ± 51	388 ± 55	$p = 0.961$	397 ± 75	402 ± 74	$p = 0.808$
C4	Averaged N400 (μV)	6.64 ± 3.03	8.55 ± 5.70	$p = 0.193$	2.56 ± 3.61	5.75 ± 4.56	**$p = 0.017$**
	Peak (μV)	9.93 ± 3.61	13.02 ± 7.17	$p = 0.119$	6.60 ± 4.35	10.57 ± 6.46	**$p = 0.020$**
	Latency (ms)	371 ± 58	383 ± 51	$p = 0.444$	395 ± 78	402 ± 75	$p = 0.757$
P3	Averaged N400 (μV)	5.52 ± 3.02	7.11 ± 4.41	$p = 0.279$	2.28 ± 3.38	4.33 ± 3.65	$p = 0.075$
	Peak (μV)	8.72 ± 3.16	11.13 ± 5.13	$p = 0.102$	5.81 ± 4.45	9.19 ± 4.08	**$p = 0.007$**
	Latency (ms)	390 ± 48	383 ± 57	$p = 0.616$	385 ± 76	411 ± 71	$p = 0.228$
Pz	Averaged N400 (μV)	6.75 ± 3.13	7.89 ± 5.03	$p = 0.769$	2.74 ± 3.15	5.13 ± 3.71	**$p = 0.016$**
	Peak (μV)	10.04 ± 2.96	12.52 ± 5.29	$p = 0.128$	6.23 ± 3.77	10.17 ± 4.66	**$p = 0.001$***
	Latency (ms)	385 ± 55	375 ± 62	$p = 0.554$	358 ± 84	409 ± 74	**$p = 0.030$**
P4	Averaged N400 (μV)	7.39 ± 3.06	7.72 ± 4.91	$p = 0.927$	3.68 ± 2.87	4.86 ± 3.72	$p = 0.248$
	Peak (μV)	10.32 ± 3.24	11.40 ± 5.35	$p = 0.533$	7.13 ± 3.10	9.49 ± 4.21	**$p = 0.021$**
	Latency (ms)	374 ± 59	384 ± 60	$p = 0.574$	336 ± 83	386 ± 92	**$p = 0.049$**

MwA patients who have migraine with aura, *HCs* healthy controls, *μV* microvolts, *ms* milliseconds, *Averaged N400* averaged amplitudes from N400 effect window (260–460 ms), * – significant after FDR correction

Further, a comparison in terms of the N400 effect revealed that topography differs between groups (Fig. 3), showing that the N400 effect in the HCs group is localized around the Cz site and in the MwA group is more widespread over central sites with extension towards posterior and frontal sites. Also, differences are noticed on the averaged difference ERP waveforms, where the P600 effect was significantly stronger in the HCs group relative to the MwA group at the Pz (6.52 ± 2.57 vs. 3.50 ± 3.15, $p = 0.001$) and P4 (5.86 ± 2.79 vs. 3.95 ± 3.64, $p = 0.040$) sites. The peak latency of the N400 and P600 effects at all investigated sites did not significantly differ between these two groups.

For the purpose of deeper explorative analysis, comparisons between groups in both experimental conditions at the relevant electrodes were conducted by using averaged amplitudes of consecutive time instants. Figure 4 shows the mapping of statistical significance between groups for certain time bins. The interval of difference is considered significant only if statistically significant differences occurred in more than 3 consecutive time bins (corresponding to intervals longer than 60 ms duration) to filter out potential statistical artifacts in line with expected electrophysiological signal properties [19]. The obtained results revealed no intervals of statistical significance for the congruent condition and multiple intervals of statistical significance for the incongruent condition between groups. The earliest onset of statistical significance for the incongruent condition was observed centrally at C3 and C4 channels, starting around 120 and 140 ms, respectively. The obtained intervals of statistical significance for incongruent condition per channel are: Fz (220–520 ms and 580–680 ms), F4 (280–480 ms), C3 (120–200 ms and 280–600 ms), Cz (380–600 ms), C4 (140–240 ms and

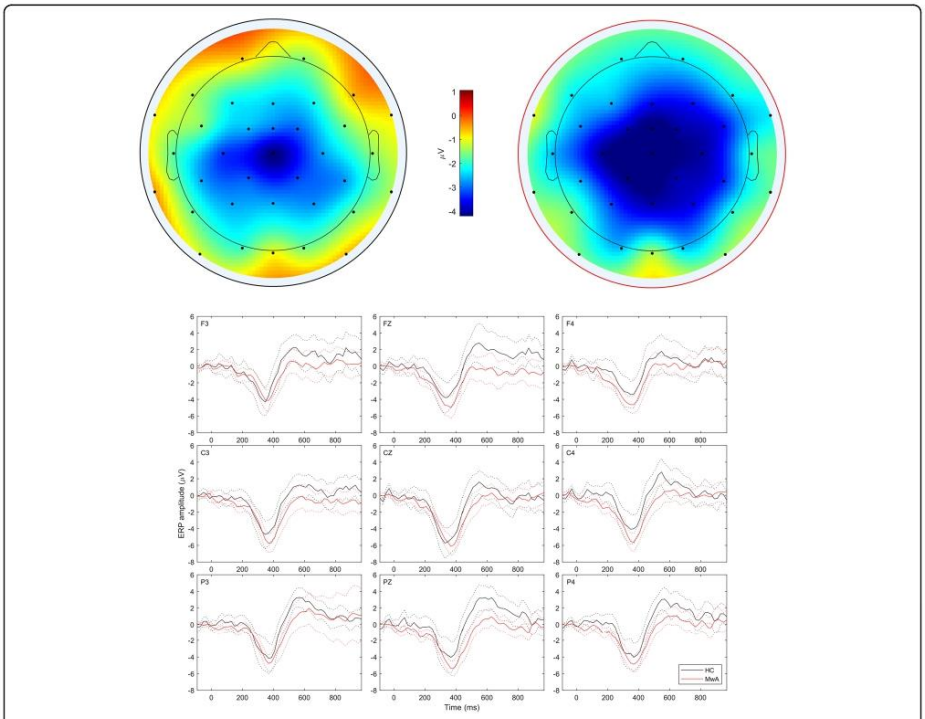

Fig. 3 The difference waves of N400 effect and topography maps derived from the grand averaged ERPs elicited by task stimuli in MwA and HCs. The N400 component (topographical plot of mean amplitude in 260–460 ms window) is widely distributed over frontal, central, and parietal areas with the center at Cz in MwA patients (right topography), whereas in the HCs group (left topography) N400 component is distributed over central and parietal areas

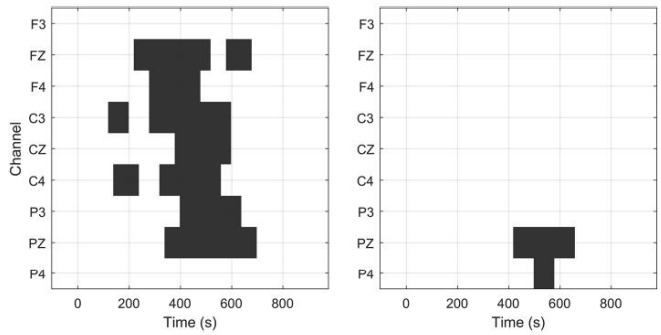

Fig. 4 Intervals of significance between groups for incongruent stimuli (black color) and nonsignificant intervals (white color). The left graph shows the intervals for incongruent ERPs and the right graph for difference waveforms. The y-axis marks individual channels and the x-axis time points in (ms), where 0 marks the priming onset

320–540 ms), P3 (400–620 ms) and Pz (340–700 ms). Also, the results reveal two intervals of significance for difference waves at channels Pz (420–640 ms) and P4 (500–580 ms).

Discussion

In this study, we used two experimental conditions, words that match or mismatch with presented pictures, to study semantic processing based on the N400 effect in MwA patients. The main focus was to investigate the N400 component elicited by the incongruent stimulus because there is no previous data about this effect in MwA patients, although it is known that MwA patients frequently have dysphasia during attacks [8] and certain difficulties in language processing during the interictal period were previously noted also [10]. Our analysis showed that MwA patients had responses of lower amplitudes (higher ERP negativity) to incongruent stimuli relative to HCs, although the N400 effect (quantified by difference waveforms) did not differ between examined groups.

The N400 effect was registered in a difference wave derived from incongruent and congruent ERP waves and was successfully elicited in both groups, as expected for an effect that is known to be robustly produced by all manner of semantic incongruencies [20]. The current N400 effect, in a time window between 260 and 460 milliseconds after the onset of the target, exhibited a characteristic central–parietal spatial distribution in the HCs group that resonates with previous studies conducted on healthy populations [21]. In the MwA group, there is additional distribution towards frontal regions, although there was no interaction between the N400 effect and groups, which is rather expected because violation of this effect, for cross-modal picture-word matching tasks, is present only in a severe form of mental diseases, such as schizophrenia [22]. A region x laterality x group interaction analysis showed that the difference between groups was strongest in the central and right-frontal regions, while in other regions there was a trend towards the same pattern but differences did not reach significance, although it is quite noticeable on the topography for MwA patients (Fig. 3). This was further confirmed by exploratory analysis of time intervals of statistical significance in 20 ms time bins which revealed the presence of intervals of statistical significance between groups in the central, right-frontal and left-posterior regions, for the incongruent condition. Since characterizing N400 topography across the scalp has proven difficult due to overlapping ERP components of the response to different types of stimuli [11], we could only assume that obtained different scalp topographies within the N400 window, between the groups, are the result of either a different network of cortical regions influenced by MwA pathophysiology [20] or different level of activation within the same network. Moreover, the fact that different sensory stimuli (inputs) elicit N400 systematically, but with topographic and morphological differences, implicates that the N400 component is modality dependant but not a modality-specific neural marker of processing in a distributed semantic memory system [11]. In the context of this study, the obtained morphological and topographic differences may be attributed to complex dysregulation of sensory processing in migraine. Moreover, since we have observed significant differences between the groups only for incongruent condition, our results suggest that disorder of sensory processing in MwA patients may not affect solely the low level sensory integration, but could expand to and potentially disrupt meaning construction.

Analysis of peaks and their latencies on sites of interest showed significantly lower peak amplitudes (C3 and Pz) in MwA patients during the incongruent stimuli, while latencies did not differ between groups in both experimental conditions. This pattern was visible on most of the investigated sites, although it did not reach the threshold after correction for multiple comparisons. This result can reflect, from a physiological level, smaller post-synaptic potentials and/or less temporal synchrony among the generating neurons which influence the N400 component during incongruent stimuli [11]. Combining ERP studies with functional neuroimaging techniques might reveal the real cause of these differences.

Furthermore, sophisticated analysis of the consecutive time instants confirmed our previous analyses that incongruent stimuli yield significant differences in MwA patients relative to HCs (Fig. 4). It is important to note that the congruent stimuli follow a similar pattern, although differences were not significant. Having that in mind, it can be self-explanatory why the N400 (analysis of difference waves) effect did not differ between MwA patients and HCs [23]. Moreover, these findings are similar to a study that investigated temporal lobe epilepsy and found reduced amplitude in both congruent and incongruent conditions [24]. However, these findings should be verified on other MwA populations to allow such comparisons between two pathological conditions.

From Fig. 4, it can be seen that other time windows differ between groups at a subset of selected electrodes. This finding required further analysis of ERP components where amplitude reduction during the incongruent experimental condition in MwA patients was also significant relative to HCs. More precisely, a wave that was peaking around 550–600 milliseconds showed lower peaks in the MwA group. These findings, together with lower amplitude in the N400 component, could imply that MwA patients had increased demands on semantic processing, implying possible disruption in the initial integration of visual inputs and comprehension of information associated with word processing and recognition [11]. Moreover, the so-called P600 component may reflect an additional monitoring process of semantic integration, reflecting the evaluation of whether the picture and word matching were appropriate or not [19]. P600 effect was significantly decreased in MwA patients at the posterior region, which could suggest an abnormal response to incongruent stimuli during the late phase of semantic processing as well. Knowing that MwA patients have abnormal sensitivity to environmental stimuli that can cause nonpainful discomfort [25], the P600 effect and this experimental condition could serve for future ERP studies designed to investigate MwA and their subtypes [14].

Admittedly, this study is limited by the lack of comparison with migraine patients without aura, thus our results could not be interpreted as specific for MwA patients. Given that there is a noted difference between MwA and MwoA in ERP studies that investigated the P3 component [26], we also can expect some difference between MwA and MwoA relative to the N400 component as well. Moreover, other electrophysiological techniques, such as visual and somatosensory evoked potentials, demonstrated various changes in MwA patients compared to MwoA [27], together with ERPs that elicit P3 and N400 components neurophysiological techniques could be of great help in the search for the pathophysiological basis of migraine aura. The strength of the study is the relatively large number of examined patients and sophisticated analysis of the data. Moreover, these are the first findings using the above described experimental conditions, which should establish the path for investigation of the influence of different MwA characteristics, such as headache intensity, aura manifestation, MwA frequency, depression severity and used medications, on the cognitive and semantic processing in MwA patients [6]. If any of these factors are found to be related to changes in ERPs elicited from the N400 paradigm, then the N400 component could serve as a tool for daily practice in a headache clinic as an additional measure for monitoring patients status, regarding symptoms changes in frequency and severity, follow up of the response to a specific treatment, or look for cognitive changes during MwA attack. The proposed experimental protocol is short (of 5 min average duration per subject) while the EEG measurements preparation procedure can be shortened by selecting only several EEG channels for analysis which is proven feasible in this study. This further contributes to the potential usability of this method in daily clinical diagnostic practice.

Conclusions

Overall, the present pattern of the N400 component provided new evidence for the dysfunction of cognitive and semantic function in MwA patients during the interictal phase. Also, incongruent stimuli could serve as a potential new method for investigation of MwA pathophysiology and their consequence on cognitive and semantic processing.

Abbreviations

ERP: Event-related potentials; MwA: Migraine with aura; HC: Healthy controls; EEG: Electroencephalography; FDR: The false discovery rate; ms: Milliseconds

Acknowledgments

Not applicable.

Authors' contributions

IP contributed to the study aim, design, acquisition, analysis, interpretation and drafting of the manuscript. VJ contributed to the acquisition, analysis and interpretation of data. VK contributed to the study design, interpretation

and revising of the manuscript. AS contributed to the study aim, design, analysis, interpretation, drafting of the manuscript and supervision. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Medical Ethics Committee of the Neurology Clinic, Clinical Center of Serbia (reference number: 23–690), and was conducted following the Declaration of Helsinki. Informed consent forms were completed by all the participants after receiving an explanation of the study.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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8. SPISAK SKRAĆENICA

EEG – Elektroencefalografija
ERP - Događajem izazvani kortikalni potencijali
MwA – migrena sa aurom
MwA-k - osobe koje imaju migrenu sa kompleksnom aurom
MwA-v - osobe koje imaju migrenu sa samo klasičnom vizuelnom aurom
P3-č - P300 talas tokom čestih stimulusa
P3-d - vrednost dobijena razlikom između P300 talasa tokom retkih i čestih stimulusa
P3-r - P300 talas tokom retkih stimulusa
SSEP - Somatosenzorno evocirani potencijali
VEP - Vizuelno evocirani potencijali
ZI - zdravi ispitanici

9. BIOGRAFIJA AUTORA

Naučni saradnik dr Igor Petrušić rođen je 13.7.1987. godine u Atini, Grčka. Završio je osnovnu i srednju školu u Beogradu. Diplomirao je na Medicinskom fakultetu Univerziteta u Beogradu 2012. godine, sa završnim radom iz oblasti neurologije „Učestalost i tip poremećaja viših kortikalnih funkcija tokom aure migrene" pod mentorstvom prof. dr Jasne Zidverc-Trajković. Na istoj ustanovi 2014. godine završio je specijalističke akademske studije sa tezom iz nuklearne medicine „Poređenje hibridne pozitronske emisione tomografije sa kompjuterizovanom tomografijom i multidetektorske kompjuterizovane tomografije u otkrivanju metastaza kod nesitnoćelijskog karcinoma pluća" pod mentorstvom prof. dr Dragane Šobić-Šaranović. Na Medicinskom fakultetu Univerziteta u Beogradu 2017. godine odbranio je doktorsku tezu „Korelacija nozologije i savremenih neurovizuelizacionih nalaza kod migrenske aure u interiktalnoj fazi" pod mentorstvom prof. dr Ružice Maksimović, prof. dr Marka Daković a i prof. dr Jasne Zidverc-Trajković i stekao zvanje doktor medicinskih nauka iz uže oblasti radiologija i nuklearna medicina. Specijalizaciju iz radiologije završio je 2018. godine. Od 2017. godine zaposlen je kao naučni saradnik na Fakultetu za fizičku hemiju Univerziteta u Beogradu (Laboratorija za naprednu analizu neuroimidžiga). Učestvovao je na projektu Ministarstva prosvete, nauke i tehnološkog razvoja („Biomarkeri u neurodegenerativnim i malignim procesima" - III 41005). Radio je kao saradnik u nastavi na predmetima Patofiziologija, Patofiziologija 1, Patofiziologija 2 i Medicinska terminologija na Farmaceutskom fakultetu Univerziteta u Beogradu. Predavač je na doktorskim studijama Fakulteta za fizičku hemiju (predmet: Napredne metode analize radioloških snimaka) i doktorskih studija iz Biofizike pri Univerzitetu u Beogradu (predmeti: 1 - Neurobiofizičke tehnike i 2 - Metode oslikavanja bioloških sistema magnetnom rezonancijom). Student je doktorskih studija „Biomedicinsko inženjerstvo i tehnologije" na Univerzitetu u Beogradu, gde se bavi analizom događajem izazvanih moždanih potencijala kod osoba sa migrenom sa aurom, sa mentorima prof. dr Ljubicom Konstantinović i dr Andrejem Savićem, višim naučnim saradnikom. Autor je devetnaest naučnih radova u međunarodnim časopisima, četiri kritike i polemike u međunarodnim časopisima, pet predavanja po pozivu i dvanaest konferencijskih saopštenja u izvodu.

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