frontiers in Neuroscience

ORIGINAL RESEARCH
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INTRODUCTION

sc, zop, ren a s a psyc, atr c d sorder t, at s assoc ated wt, var ous c n ca sy pto s sus, as aud tory a, a uc nat ons parano d de us ona t, ous, ts d sorgan zed t, n ng and d sturbances of se f. D agnost c and tat st ca Manua of Menta D sorders Fou t, Ed t on . A er can Psyc, atry Assoc at on , , On tsu a et a – –One of t, e cogn t ve dysfunct ons n peop e wt, sc, zop, ren a s fac a process ng at bot, t, e be, av ora . C, en Ma, er et a – . and p, ys o og ca eve s. Herr ann et a – On tsu a et a – . sunoda et a – Ma, er et a – . E, eng et a – . – Many recent stud es, ave s, own t, at peop e wt, d agnos s of sc, zop, ren a often ex, b t pa r ents n fac a express on recogn t on w, s, are suggested to be re ated to poor soc a funct on ng . M s, a opou ou et a – Ko, er et a – Mendoza et a – Csu y et a – McC eery et a – –, e percept on of fac a express ons w, s, prov des a funda enta e ot ona ana ys s of t, e enta ntent on of a person s found to be abnor a n peop e wt, sc, zop, ren a. for rev ew see McC eery et a – –Prev ous stud es, ave a n y focused on t, e recogn t on or e ory of fac a express ons n pat ents wt, sc, zop, ren a. Gu au e et a – –However a recent study revea s t, at t, e v sua s a s, negat v t es . vMMNs evo ed by c, anges of fac a express ons cou d a so be abnor a n sc, zop, ren a. Csu y et a – – .

e ated to auto at c process ng MMN s de ned as t, e d erence between t, e potent a s evo ed by dev ant . nfrequent and standard . frequent st u . N t nen et a – – Accu u at ng ev dence, as suggested t, at t, e var at on of not on y t, e ow eve features of v sua st u sus, as co or ot on or spat a frequency but a so, g, eve fac a express ons cou d e ect ve y evo e vMMN. Pazo A varez et a – usac et a – E, ao and L . Cz g er Ast a nen and H etanen L et a – –Prev ous stud es, ave s, own t, at a r g, t poster or fac a express on vMMN e c ted by sad and, appy

TABLE 1 | Basic demographic and descriptive characteristics in both groups.

	Patients with schizophrenia (n = 23)	Healthy control subjects (n = 23)	
Gender (male/female)	12/11	12/11	1.0[a]
Education (years)	12.9 (2.6)	12.5 (3.5)	0.707[b]
Average family income (RMB/per year)	5079.2 (3724.9)	6291.67 (3473.2)	0.249[b]
Handedness (right/left)	23/0	23/0	
Schizophrenia subtypes: Paranoid/Undifferentiated	16/7	N/A	
Duration of illness (years)	8.7 (6.3)	N/A	
PANSS total	52.4 (12.4)	32.3 (1.5)	0.000[b]
PANSS positive symptoms	13.3 (5.4)	7.4 (0.7)	0.000[b]
PANSS negative symptoms	11.2 (4.2)	7.2 (0.4)	0.000[b]
PANSS general symptoms	27.9 (6.2)	17.7 (1.2)	0.000[b]
Antipsychotic medication (Atypical/Typical)	21/2	N/A	
Chlorpromazine equivalent (mg)	556.5 (350.2)	N/A	
PSP	60.5 (9.9)	89.1 (4.3)	0.000[b]

[a] *Binomial.*
[b] *T-test.*
PANSS, Positive and Negative Syndrome Scale.

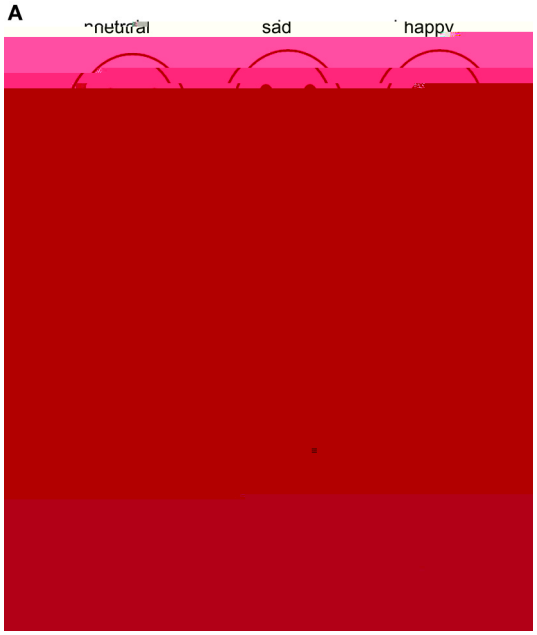

FIGURE 1 | Illustration of experimental stimuli and procedure used in the present study. **(A)** Examples of schematic face stimuli that contain three facial expressions: neutral, sad, and happy. **(B)** Illustration of the experimental procedure. The neutral faces served as standard stimuli and happy and sad faces as deviant stimuli. The task was to judge the change in size of the fixation cross ("+") in the visual center.

part c pants rece ved pay ents and prov ded wr tten nfor ed consent for t, e r part c pat on–

Stimuli and Procedure

As presented n a prev ous study conducted by t, s reseat, group . Xu et a – to reduce t, e e ect of ow eve features d erent s, e at c faces w t, neutra sad and , appy express ons were used and nd v dua s, e at c faces were nc uded for ea, st u us type . see an exa p e n **Figure 1A** –Modu ated by s, ang ng t, e s, ape of and t, e d stance between t, e fac a features ea, type of st u us nc uded ode s– , e v sua st u were presented on bo t, s des of t, e xat on and t, e durat on of exposure was s w t, a s nter st u us nterva and a v sua ang e of ° × ° – , e t, ree st u us oddba parad g was used– **Figure 1B** s, ows t, e exper enta procedure– , e neutra faces served as standard st u and , appy and sad faces as dev ant st u o estab s, a sensory e ory pattern standard st u . neutra faces were presented at t, e beg nn ng of a st u us sequence and w t, no ess t, an two standards between consecut ve dev ants– , e part c pants were as ed to focus on t, e xat on crosses w t, a s, anged s ze w, s, were a ways presented w t, out faces to avo d otor generated art facts– Four b oc s were conducted w t, tr a s for ea, . standard neutra faces dev ant , appy and sad faces – , e tas perfor ed by t, e part c pants was to dge t, e s, ange n s ze of t, e xat on cross . + n t, e v sua center– Pract ce tr a s were conducted before t, e test tr a s– , ere was a n brea between b oc s–

Electrophysiological Recording

EEG was recorded cont nuous y by a set of Ag AgC e ectrodes p aced accord ng to t, e syste nc ud ng F Fz F C Cz C P P Pz P P PO PO O Oz and O – E ectroocu ograp y . EOG was recorded v a e ectrodes p aced on t, e b atera externa cant, and t, e eft nfraorb ta and supraorb ta areas to on tor for eye ove ents and b n s– Bot, EEG and EOG were sa p ed at Hz w t, a - Hz band pass us ng a Neuroscan NuA ps d g ta a p ers syste . Neuroscan Labs E Paso X – , e t p of t, e nose was used as reference dur ng record ng– I pedances of a e ectrodes were ept be ow Ω–

Data Analyses

, e pre process ng of t, e e ectrop ys o og ca data was conducted by t, e funct ons of t, e EEGLAB too box . De or e and Ma e g n MA LAB env ron ent– Bot, average reference . A E and approx ate zero reference . E . Yao were conducted o ne to generate two ong ter EEGs– , e A E was conducted by t, e **reref** funct on fro EEGLAB too box . De or e and Ma e g and t, e E was conducted by t, e **rest_refer** funct on fro www-neuro-uestc-edu-cn- rest– , ese ong ter EEGs of ea, e ectrode were rst y tered by a band pass ter . – Hz and t, en seg ented nto epo s fro to s around t, e onset– , e base ne correct on was conducted w t, n t, e t e w ndow of to s– , e epo s s t, at conta ned ore

t, an ± μ EOG potent a were re cted as art facts–, e rest of t, e epoc, s were t, en averaged and ow pass tered . cut o frequency = Hz to obta n two groups of E Ps for A E and E et, ods respect ve y–, e a p tudes of ear y v sua E P co ponents . P and N were ana yzed to co pare t, e pr ary sensory process ng n t, e two groups–, e vMMNs were obta ned by subtract ng E Ps to standard st u . neutra faces fro E Ps to dev ant st u . sad or, appy faces for ea, fac a express on–

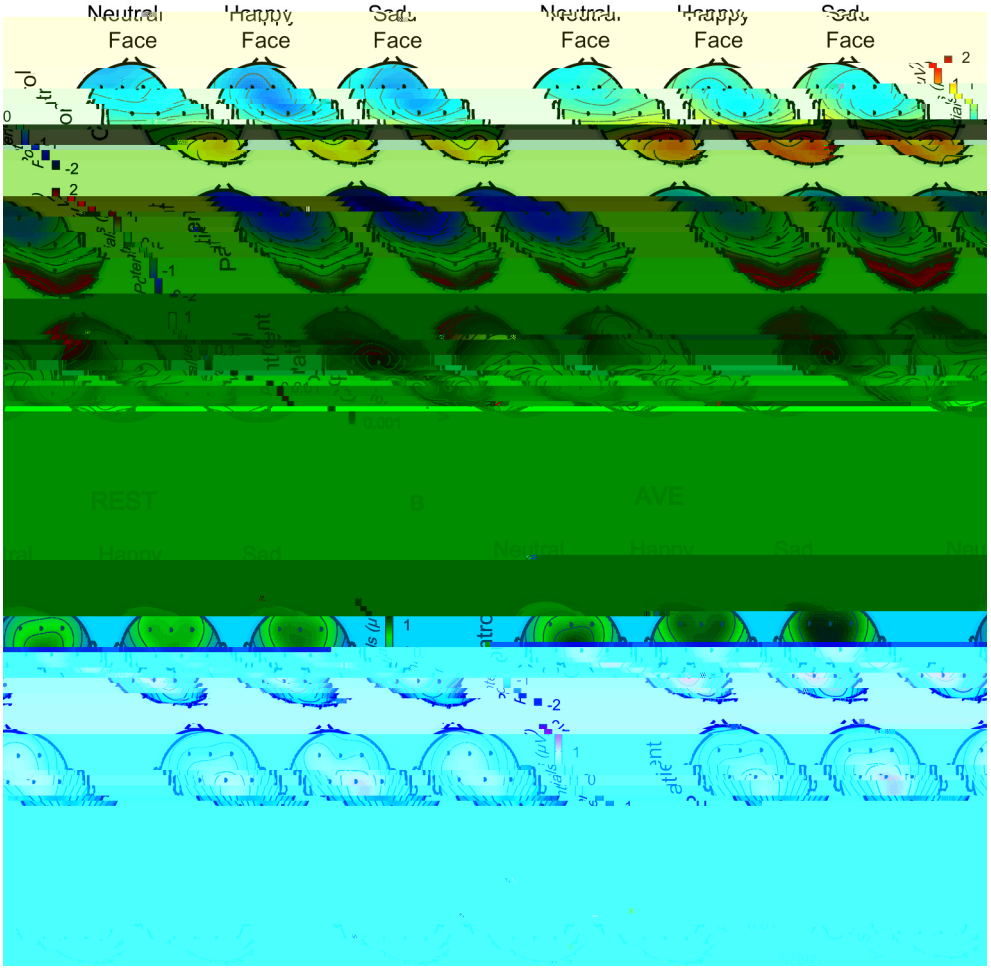

FIGURE 3 | Comparison of face evoked topographic distributions using two reference-modes (AVE and REST). **(A)** The topographic distributions of the P1 mean amplitudes (110–130 ms) under three conditions in control (top) and patient (middle) groups, and between group significance analyses (bottom, with *Bonferoni* correction). **(B)** The topographic distributions of the N170 mean amplitudes (175–195 ms) under three conditions in control (top) and patient (middle) groups, and between group significance analyses (bottom, with Bonferoni correction). AVE, average reference; REST, reference electrode standardization technique.

sad **p** = appy vs– sad **p** = PO and PO no s gn cance and E obta ned . CZ neutra vs appy **p** = neutra vs– sad **p** = appy vs– sad **p** = PO and PO no s gn cance P a p tude ad s gn cant d erence between neutra and e ot ona express ons w e n e pat ent group no s gn cance between neutra and e ot ona express ons was found– No er s gn cant **post-hoc** resu ts were found– ese resu ts de onstrated at bo e E and A E ods cou d revea a centra do nant face express on spec c P co ponent n ea y contro s w fa ed to d st ngu s neutra and e ot ona express ons n zo ren c pat ents–

For N a p tudes no s gn cance of any a n e ect or nteract on e ect was found . a **p** > –**Post-hoc** resu ts w **Bonferoni**

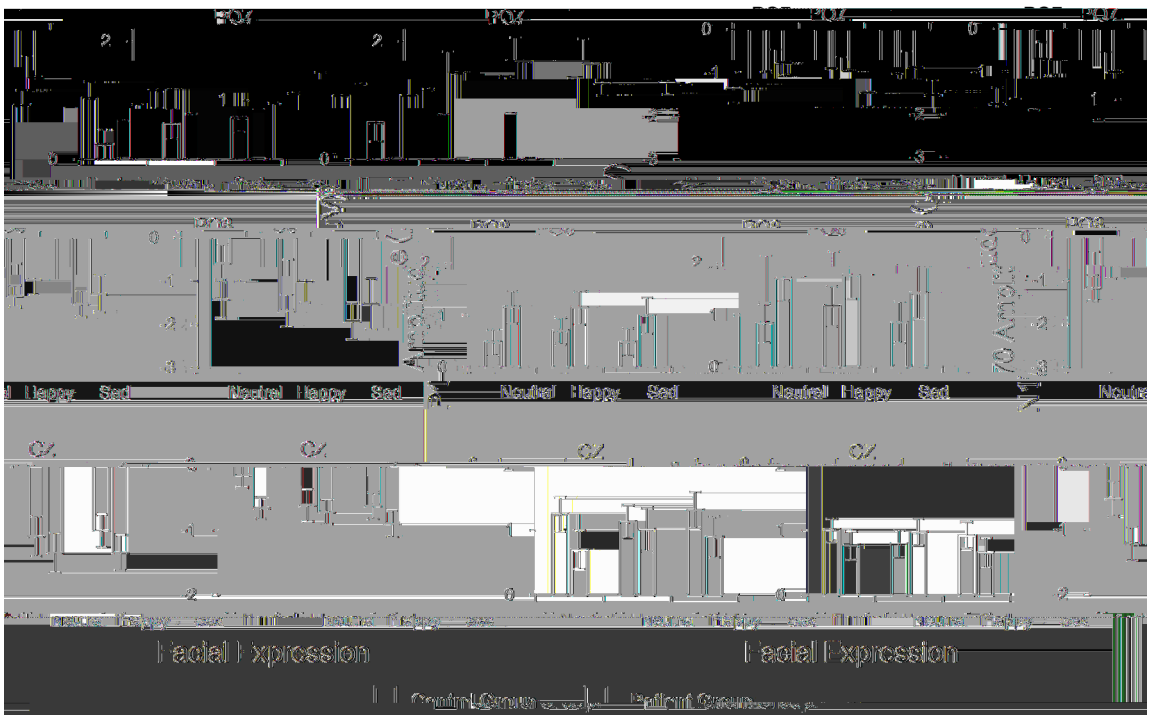

FIGURE 4 | Comparisons of P1 **(A)** and N170 **(B)** amplitudes in patient and control groups in temporo-occipital electrodes (PO7 and PO8) and central electrode (CZ) using two reference-modes (AVE and REST). White bars, control group; Gray bars, patient group. AVE, average reference; REST, reference electrode standardization technique.

e te poro occ p ta e ectrodes . PO and PO and centra e ectrode . CZ – Co pared to e A E obta ned vMMN e E obta ned vMMN gave g er evo ed potent a s around te poro occ p ta e ectrodes . PO and PO and ower evo ed potent a s n CZ– e resu ts of topograp c ana yses s owed at for bo reference ods e d str but ons of vMMN were concentrated n e centra areas n contro group but not n pat ent group . to s **Figure 6** – Fu er ore e d erences between topograp c d str but ons of contro s and pat ents were a so concentrated n e centra areas . **Figure 6** bo to pane s –

o eva uate e group and st u at on e ects on e vMMN potent a w d erent reference te no og es . Group pat ent and contro × . M s ats ed fac a express on appy and sad × . eference type A E and E ree way xed easured ANO As were conducted respect ve y– ree e ectrodes PO PO and CZ were nvo ved n e ana ys s represent ng e te poro occ p ta and centra areas respect ve y–

e resu ts s owed at ne er a n e ect of M s ats ed fac a express on nor eference type was s gn cant . a $p >$. – gn cant Group e ect was found n centra e ectrode CZ F =

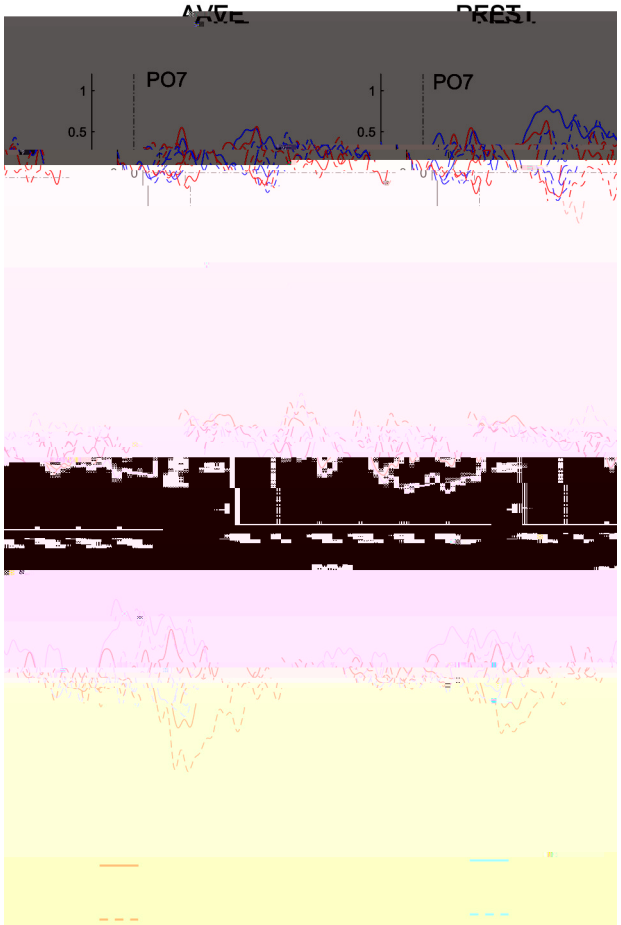

FIGURE 5 | Comparison of face evoked vMMNs using two reference-modes (AVE and REST). Waveforms of temporo-occipital electrodes (PO7 and PO8) and central electrode (CZ) ERPs evoked using three stimulus conditions (neutral, happy, and sad facial expressions) in both control and patient groups are also compared. Solid lines, control group; Broken lines, patient group; AVE, average reference; REST, reference electrode standardization technique; vMMN, visual mismatch negativity.

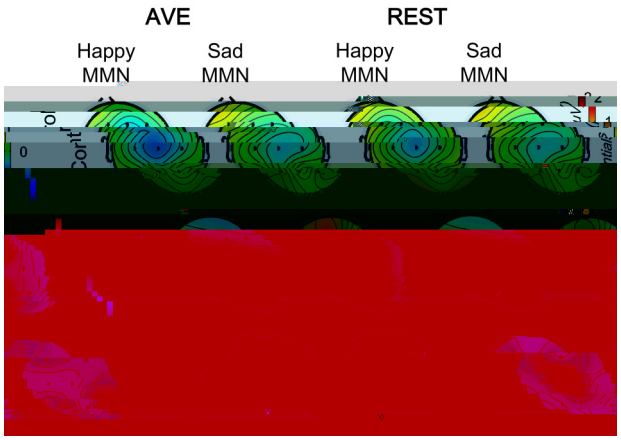

FIGURE 6 | Comparison of vMMN topographic distributions using two reference-modes (AVE and REST). The topographic distributions of facial expression vMMNs (100–400 ms) under two conditions (happy and sad deviant) in control (top) and patient (middle) groups, and between group significance analyses (bottom, with Bonferroni correction). AVE, average reference; REST, reference electrode standardization technique.

at n PO n on y e pat ent group. $p =$ for bo A E and E ese resu ts suggested a r g e sp ere do nance of sad MMN n peop e w sc zop ren a–

DISCUSSION

Face process ng dysfunct on as been w de y exp ored n prev ous stud es . Herr ann et a – On tsu a et a – C en sunoda et a – Ma er et a – E eng et a – owever on y a few ave co pared v sua s a responses e c ted by tas rre evant fac a express ons between ea y contro s and pat ents w sc zop ren a rban et a – Csu y et a – – In e current study a ou e perfor ance n e detect on tas d d not d er between e two groups of part c pants bo e A E and E obta ned ear y v sua E Ps and vMMN were d erent between e pat ent and contro groups– Our ypo eses were c ar ed by e nd ngs at . ear y v sua dysfunct on n process ng e ot ona faces ex sted n peop e w sc zop ren a . vMMN s gn cant y reduced n peop e w sc zop ren a n co par son to ea y part c pants w s ad a r g t e sp ere do nance and . genera y E was as good as A E n revea ng e neurop ys o og ca d erences between peop e w sc zop ren a and ea y peop e w e on y e E obta n vMMN revea ed a s gn cant d erence between appy and sad s a st u n sc zop ren c pat ents–

Expressional Face-Evoked P1 and vMMN Dysfunction in Schizophrenia

Genera y n e current study bo A E and E et ods cou d e ect ve y d st ngu s e express ona face evo ed P and vMMNs between ea y contro s and sc zop ren c pat ents w s were n accordance w prev ous stud es of ear y v sua E Ps. Herr ann et a – On tsu a et a – sunoda et a – Ma er et a – E eng et a – and vMMNs rban et a – Csu y et a – us ng A E reference–

A recent study as suggested a e under y ng processes of ear y vMMN re ect e neurona refractory e ect w e vMMN re ects e e ory co par son based ange detect on e ect . K ura et a – – upport ng s ssue ere s ev dence a e ear er vMMN co ponents cou d be evo ed under tas rre evant st u represent ng an auto at c ange detect on an s . Ast a nen and H etanen Mae awa et a – – e resu ts of e current study nd cated a funct ona d erence n auto at c detect on of anges n fac a express on n sc zop ren c pat ents–

I portant y e vMMNs were s gn cant y reduced n pat ents w sc zop ren a co pared to ea y contro s nd cat ng e dysfunct on of process ng tas rre evant fac a

express ons w, en, appy express ons acted as s a c, st u – Csu y et a –. nvest gated, e abnor a ty n, e vMMN e c ted by unexpected fac a express ons n pat ents w, sc, zop, ren a and found, at s a c, responses to bo, fearfu and, appy e ot ona faces were s gn cant y pa red n pat ents co pared to age a c, ed contro s– A, oug, , e conc us on of, e Csu y et a –. study s s ar to, at of, e present study, ere are severa , odo og ca d erences– For nstance n, s study on y parano d and und erent ated sc, zop, ren c pat ents w, e ot ona abnor ty were recru ted to ore re ab y nvest gate, e processes under y ng fac a recogn t on–

It s, ou d be noted, at e ot ona recogn t on was not requ red n, e present study– Csu y et a –. proposed, at process ng de c ts of e ot on g, t ed ate, e assoc at on between auto at c nfor at on process ng de c ts n, e da y ves of peop e w, sc, zop, ren a. Csu y et a – –However, s ssue needs fu, er nvest gat on– In add t on sc, e at c e ot ona faces were used as exper enta st u to n ze, e var at ons of actua faces nc ud ng ow process ng eve fac a features as we as, e poss b ty of gender e ects– Prev ous nd ngs, ave nd cated, at sc, e at c faces ay be usefu for c n ca study and app cat on because of, e r s p c ty co pared to actua, u an faces . g, t et a – – A, oug, sc, e at c e ot ona faces, ave been used n severa stud es . C, ang et a – Xu et a – and s ar vMMN resu ts, ave been reported w, rea faces t s necessary to use rea faces to fu, er nvest gate, s ssue–

In add t on, e current study a so revea ed, at, e sad vMMN was s gn cant y arger n, e r g, t, an, e eft te poro occ p ta area n sc, zop, ren c pat ents– Because prev ous neuropsyc, o og ca stud es, ave suggested, at, e r g, t, e sp, ere s re at ve y super or to, e eft n, e percept on of fac a express on . Manda and ng, , Borod , Manda et a – , espec a y negat ve ones . Dav dson et a – , Manda et a – , , ese ev dences p y, at auto at ca y process ng of negat ve fac a e ot on g, t be pa red n sc, zop, ren c pat ents w, do nant r g, t, e sp, eres–

Choice of Reference in Clinical ERP Study

s study syste at ca y nvest gated, e face express on neurop, ys o og ca ar ers n peop e w, d agnos s of sc, zop, ren a and, ea, y contro s by co par ng A E and E referenc ng et, ods– As a co on y reco ended reference A E s conducted by averag ng a, e sca p e ectrodes– However recent stud es s, ow, at E s ore re ab e w, ow dens ty ontage . L u et a – Yao –Cons der ng, e t e costs and operat ona d cu t es ost of, e c n ca stud es, at a ed at nd ng a re ab e and e ect ve b o ar er to d st ngu s, neuropsyc, atr c pat ents fro, e, ea, y popu at on prefer a ow dens ty ontage des gn–In, e current study bo, A E and E et, ods cou d e ect ve y d st ngu s, e fac a express on evo ed E Ps and MMNs between sc, zop, ren c pat ents and, ea, y contro s n our ow dens ty ontage des gn suggest ng E s an appropr ate approac, n c n ca neurop, ys o og ca stud es w, s, cou d be app ed to arge popu at ons–

An nterest ng resu t fro, e current study was, e nd ng, at on y, e E obta ned vMMN but not, e A E obta ned vMMN revea ed a s gn cant d erence between, appy and sad s a c, st u n sc, zop, ren c pat ents but not n, ea, y contro s . **Figure 7** – Cr t ca y, s nd ng dose not d rect y suggest, at E s super or to A E– Approx ate y reconstruct ng a po nt far away fro a, e sca p e ectrodes E was suggested to be a neutra reference. Yao , Z, a and Yao , L u et a – , C, e a et a – , –, erefore E usua y ac, eves ore obj ct ve resu ts w, s, cou d poss b y, p, e s gn cance of a resu t fro, e ot, er references nc ud ng A E . an and Yao – A, oug, , e a n purpose of, e c n ca E P stud es was to revea neurop, ys o og ca d erence between pat ents and contro s prev ous resu ts obta ned w, a non zero reference sc, as A E need ore con r atory ev dence and so we reco end app cat ons of E n neurop, ys o og ca stud es of neuropsyc, atr c d sorders n, e future–

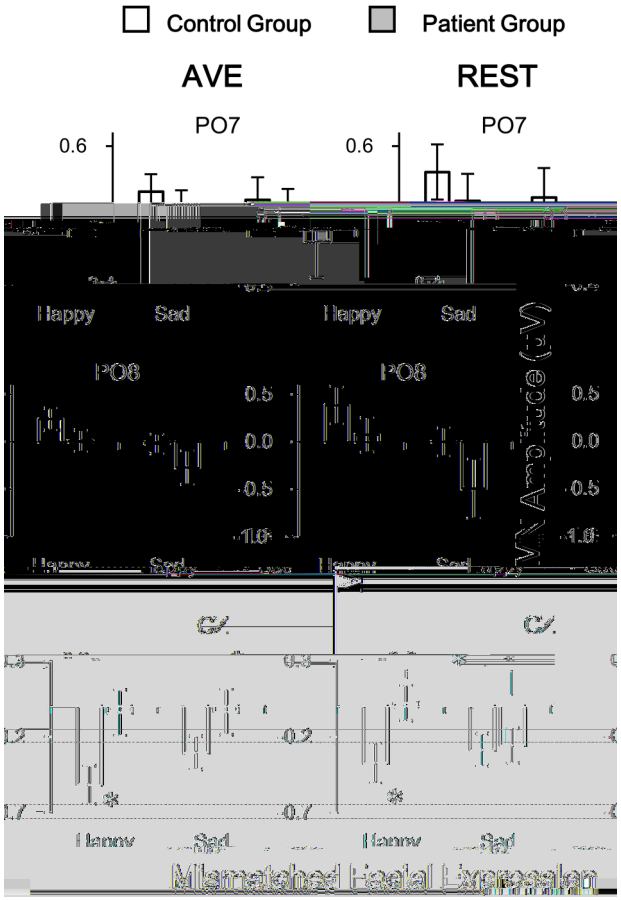

FIGURE 7 | Comparisons of vMMN amplitudes in patient and control groups in temporo-occipital electrodes (PO7e d7(i)-0.1599[illegible]6190s4018s41[illegible]1907.451604(n)-278.61()-(

AUTHOR CONTRIBUTIONS

Each of the authors HL YN JH ZH JZ and YZ designed the study and wrote the protocol. HL and YZ performed the experiments. JZ wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

ACKNOWLEDGMENTS

usac A– I on e –J– P o E– and upe –Neurodyna c stud es on e ot ona and nverted faces n an oddba parad g –**Brain Topogr.** do B B A –cb

an Y– and Yao D– – y do we need to use a zero reference eference n uences on e E Ps of aud ov sua e ects–**Psychophysiology** do psyp–

sunoda – Kanba eno – H rano Y– H rano– Mae awa– – et a – A tered face nvers on e ect and assoc at on between face N reduct on and soc a dysfunct on n pat ents w s zo ren a–**Clin. Neurophysiol.** do

rban A– Kre ace J– Masopust J– and L b ger J– sua s at negat v ty a ong pat ents w s zo ren a–**Schizophr. Res.** do res–

g t C– I– Mart s B– n L– M– F s er H– and au – L– – E anced a ygda a responses to e ot ona versus neutra s e at c fac a express ons– **Neuroreport** – do

Xu – Yang Y– ang P– un G– and ao L– –Gender d erences n preattent ve process ng of fac a express ons an E P tudy–**Brain Topogr.** do s

Yao D–. – A od to standard ze a reference of sca p EEG record ngs to a po nt at n n ty– **Physiol. Meas.** – do

s E . P . o d E e . n . v . t . t . w . e –