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*Reply*

# Introspection of UBNIN and Modified-UBNIN Algorithms for Structural MRI. Reply to Kelly et al. A Comparison of Brain-State Representations of Binary Neuroimaging Connectivity Data. Comment on "Samantaray et al. Unique Brain Network Identification Number for Parkinson's and Healthy Individuals Using Structural MRI. *Brain Sci.* 2023, *13*, 1297"

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**Abstract:** The purpose of this reply is to address the comments given by Kelly et al. on our original paper "Unique Brain Network Identification Number for Parkinson's and Healthy Individuals using Structural MRI". We agree to the inadvertent rounding pitfall in our original paper due to the non-inclusion of symbolic math toolbox (MATLAB). We now provide the actual ranges (with decimal values) of the UBNIN values of healthy individuals and those with Parkinson's disease and further observations. Upon further introspection, we propose another variant, called Modified-UBNIN (UBNIN-$M_{T,MN}$) which is highly weighted on the node with the highest network degree (i.e., connections). The italicized sentences within inverted commas are statements from Kelly et al.'s comment paper.

**Keywords:** structural MRI; UBNIN; Parkinson's disease

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We appreciate Josephine N. Kelly et al. for their interest and for taking time to investigate our work [1] in detail. We are glad our work [1] sparked a scholarly conversation. We hereby reply to all of their remarks [2], which we are sure will help clarify all their points and improve our paper's level of detail.

We proposed a novel algorithm, namely, Unique Brain Network Identification Number (UBNIN) in our study [1] for representing individual brain networks using the regional grey matter volume (rGMV in $cm^3$) from structural magnetic resonance imaging (sMRI) scans of the human brain.

We [1] used sMRI scans of each individual brain to construct respective adjacency matrix comprising binary data, where 1 represents the presence and 0 represents the absence of connections between nodes (brain regions). Further, we appreciate that Kelly et al. have proposed variants of UBNIN, naming them UBNIN-C (complete UBNIN), UBNIN-R (Rounded UBNIN), and UBNIN-T (Truncated UBNIN). However, we would also like to emphasize that UBNIN-T, as understood by Kelly et al. from our abstract, is not a truncated version of UBNIN. Rather, it is the complete UBNIN value obtained. The UBNIN value (in our original paper) lacks the fractional part due to rounding off in the intermediate steps during computation, which we have now recovered using the symbolic math toolbox in MATLAB. We have not purposely truncated any UBNIN value in the algorithm to make it manageable. The UBNIN range for the HC and PD subjects are now added in the appendix of this paper. This also explains the following query that was raised: "*Interestingly, the UBNINs shown… retrieved by decoding those UBNINs*" and "*It is not clear exactly what the authors… to understand its properties*". Additionally, we would like to mention an error in Figure 1 of Kelly et al., displaying '1′ in row 9, column 8 and in row 10, column 8. Neither Figure 1 nor 2 of our original article shows a connection between the eighth and ninth node or the eighth and tenth node.

We appreciate that Kelly et al. have provided further insights into the UBNIN by providing a comparison between the UBNIN and other methods (binary, base 10, and hexadecimal representations). However, we would like to clarify that information on the number of nodes is required for decoding in a hexadecimal way of representation, unlike what is mentioned in Table 2 of the comment paper by Kelly et al. This is because the number of digits in this representation does not imply the number of nodes. Moreover, our UBNIN method indicates the number of nodes in $UBNIN_T$, where T denotes the number of nodes in the network or columns in the adjacency matrix. Hence, extra information is already available in $UBNIN_T$, as the subscript 'T' determines the correct power of 2. Additionally, as mentioned by Kelly et al., we also obtained the same UBNIN value of 321.00597984889463987201452255249023437 5. However, this number was too long for representation, hence we showed only up to 15 digits. In response to "*Toward this end… base 10 representations of that column*", it is worth noting that we did not reorder in the way explained in the above lines to preserve the original order of nodes, as they denote specific brain regions. The sequence of nodes for each subject is hence kept identical to those of every other subject and is the same as that obtained using a standard parcellation atlas (LPBA40, [3]). Thereby, with reconstruction, no additional data would be required to map the brain regions.

We also propose that in UBNIN-$M_{T,MN}$, the MN (maximally occurring principal node) will play a major role and can be selected from the data or literature. It could be the most significant brain region differing between health and disease (e.g., substantia nigra for Parkinson's disease and superior temporal gyrus for schizophrenia).

The algorithm for generating the Modified Unique Brain Network Identification Number (UBNIN-$M_{T,MN}$) builds upon the original UBNIN algorithm with small modifications. This new algorithm uses the binary adjacency matrix (AM), illustrated in Figure 1, with 12 nodes. We evaluate the node degree, which is the number of connections (ones) in each column (node) of the AM (Step 1, Figure 1). The node with the highest degree (highlighted in pink, Step 2, Figure 1), is denoted as the principal node. This principal node for every healthy control (HC) was determined and the node with the maximum occurrence across the entire HC group is designated as the maximally occurring principal node (Figure 2). The same procedure was followed for the patients with Parkinson's disease as well.

Further, the lower triangular matrix is zeroed out, as the matrix is symmetric along the diagonal and the network is undirected (region shaded in green, Step 3, Figure 2). Now, each of the columns, from bottom to top, is assumed to be a singular binary number (Step 4, Figure 2). The values in the binarized column of the AM are then converted into their respective decimal equivalents (Step 5, Figure 2). Thus, the values (*DEC*) obtained are 0, 1, 3, 6, 13, 20, 60, 67, 1, 321, 503, and 996. The maximally occurring principal node has a *DEC* value of 3. The Modified-*UBNIN* is calculated in a similar way to the original *UBNIN*, except that the *DEC* value of the maximally occurring principal node is skipped over in the sequence (Equation (1)). The *DEC* of the maximally occurring principal node constitutes the integer part and the remaining *DEC* values were turned into a fractional value using Equation (1), where $T$ is the total number of nodes in the network, $MN$ is the maximally occurring principal node of the network, and $i$ is the node/column number of the network/binary matrix.

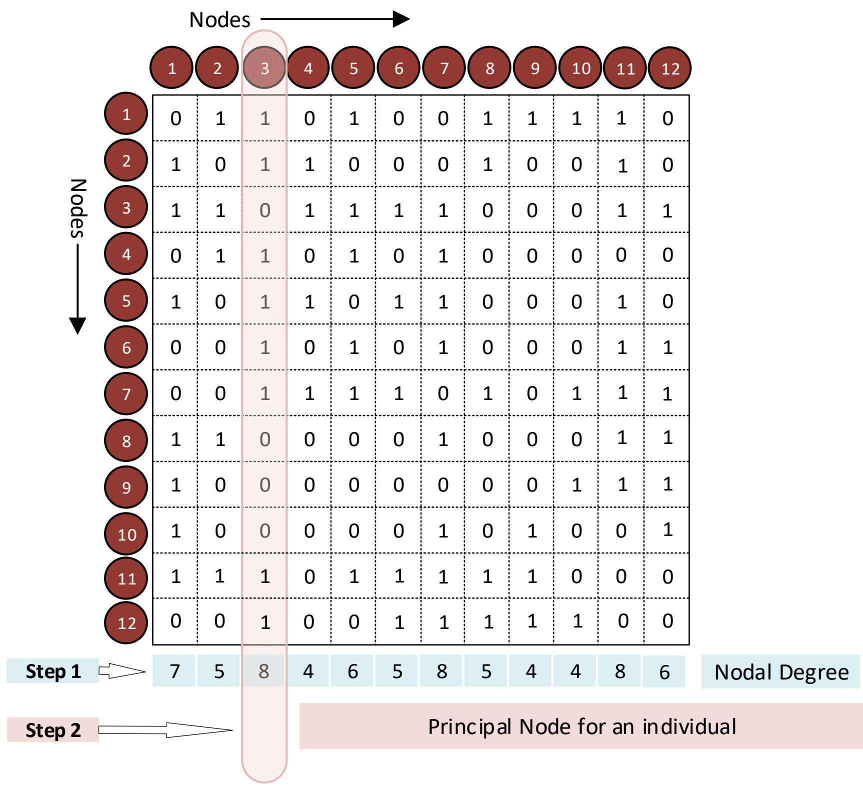


**Figure 1.** Modified-UBNIN (UBNIN-M$_{T,MN}$). Estimation of principal node.

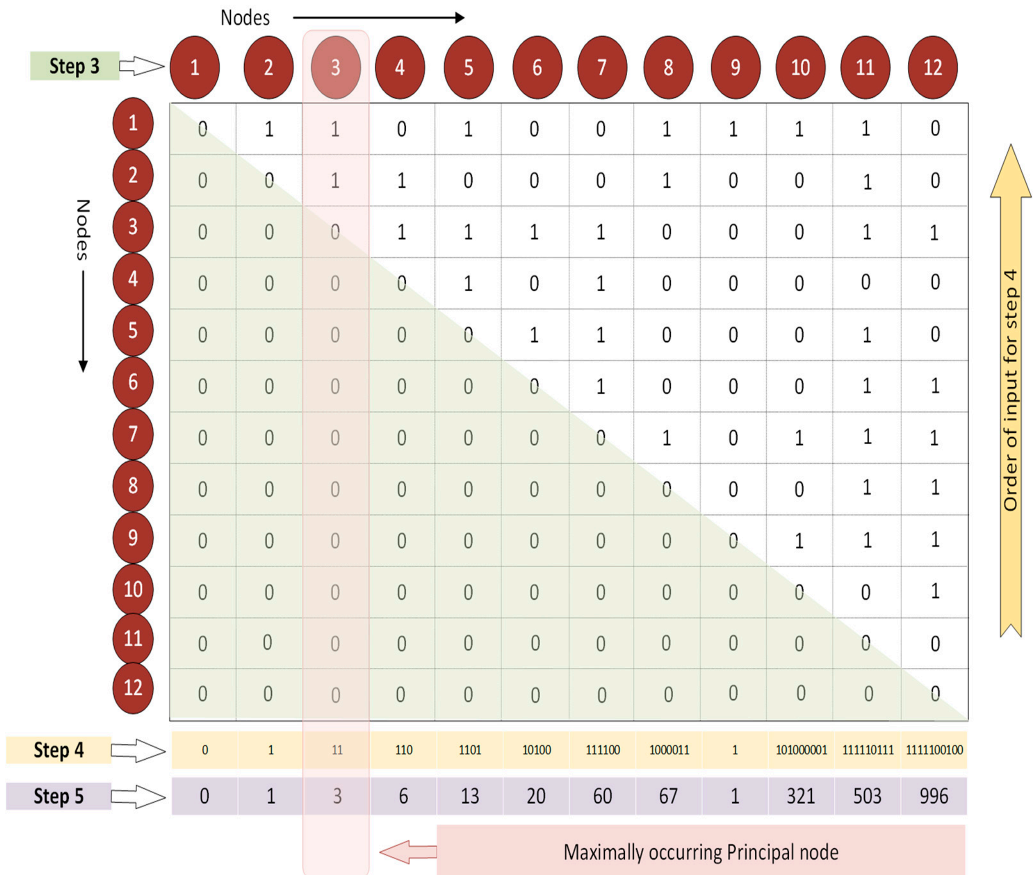


**Figure 2.** UBNIN-M$_{T,MN}$. Estimation of maximally occurring principal node and computation of Modified-UBNIN value.

$$UBNIN - M_{T=12,MN=3} = \frac{1}{2^{i=12}} \times (\frac{1}{2^{i=11}} \times |\frac{1}{2^{i=10}} \times [\frac{1}{2^{i=9}} \times \lceil \frac{1}{2^{i=8}} \times \llbracket \frac{1}{2^{i=7}} \times \{\frac{1}{2^{i=6}} \times \| \frac{1}{2^{i=5}} \times (\frac{1}{2^{i=4}} \times \langle \frac{1}{2^{i=2}} \times \lfloor \frac{1}{2^{i=1}} \times DEC(1) + DEC(2) \rfloor + DEC(4) \rangle + DEC(5)) + DEC(6) \| + DEC(7)\} + DEC(8) \rrbracket + DEC(9) \rceil + DEC(10)] + DEC(11)| + DEC(12)) + DEC(3) \quad (1)$$

Upon substituting the values in Equation (1) with the respective nodes and decimal values obtained in Step 5 of Figure 2, we obtain

$$UBNIN - M_{12,3} = \frac{1}{2^{12}} \times \Big( \frac{1}{2^{11}} \times \Big[ \frac{1}{2^{10}} \times \Big[ \frac{1}{2^{9}} \times \Big\lceil \frac{1}{2^{8}} \times \llbracket \frac{1}{2^{7}} \times \Big\{ \frac{1}{2^{6}} \times \| \frac{1}{2^{5}} \times \Big( \frac{1}{2^{4}} \times \Big\langle \frac{1}{2^{2}} \times \Big\lfloor \frac{1}{2^{1}} \times 0 + 1 \Big\rfloor + 6 \Big\rangle + 13 \Big) + 20 \| + 60 \} + 67 \rrbracket + 1 \rceil + 321 ] + 503 ] + 996 ) + 3$$

The resultant Modified-*UBNIN* (*UBNIN-$M_{T,MN}$*) for the above 12 nodes (*UBNIN-$M_{12,3}$*) is 3.243284136525345895659473878513967548542495933361351490020751953125. The expression $\frac{1}{2^i}$ starts with $i = 1$, and the equivalent *DEC* value starts with the first node of the matrix. Thus, the node with the highest degree and maximum occurrence in a cohort is highly weighted in the final *UBNIN-$M_{T,MN}$* value. The *UBNIN-$M_{T,MN}$* range for HC and PD is provided in the Appendix A.

In response to "*Finally, the word Unique... not guaranteed to differ*", we would like to convey that the UBNIN algorithm did seem to provide a unique value for every individual considered in the healthy control (HC, $n$ = 70) and Parkinson's disease (PD, $n$ = 179) groups. We have also employed the UBNIN algorithm and found distinct UBNIN values from 100,000 iterations of randomly assigned (i.e., not of a specific sparsity) 10 × 10 binary matrices. It was hence termed the 'UNIQUE' Brain Network Identification Number. This is also mentioned in our original paper (Section 4.1) [1]. Using the symbolic math toolbox in MATLAB and the Modified-UBNIN, seven HC and two PD individuals seemed to have similar values, which could be due to the similar connectomes in the brain morphology. The reason behind these similarities needs further investigation.

Considering Takao et al.'s work [4], Kelley et al. seem to suggest "*Even MRI scans for the same person... Not for each person*". Takao et al. [4] performed a longitudinal study to evaluate the inter-scanner variability and effect of MRI scanner drift. However, the uniqueness defined in our paper [1] was obtained in a cross-sectional study using T1-weighted MRI scans from a single site and single scanner. We do acknowledge that there could exist subtle differences in the UBNIN for the same person (say Mr. X) due to scanner drift when two scans are taken at a different time. We also speculate that the scans of two people (Mr. X and Mr. Y) and thereby the UBNIN could vary considerably due to the inherent grey matter differences in the human brain. However, the preceding two statements need more investigation and we invite Kelly et al. to investigate and work with us on this idea if they have access to such a dataset. In this context, it might be relevant to mention that Meda et al. found little effect of the sites (1.5 T scanner of same model at four sites) on grey matter differences in schizophrenia patients [5] using cross-sectional MRI data. Stonnington et al. [6] used cross-sectional data (six 1.5 T scanners of the same vendor at one site) to investigate the grey matter differences in Alzheimer's disease and found substantially less scanner differences than group differences. We would also like to speculate that a change in the UBNIN value might have a diagnostic viewpoint, as mentioned in Section 4.1 [1], as was observed with the UBNIN variation between the HC and PD individuals.

The size of brain regions in the LPBA40 atlas vary significantly. This may affect the connection strength in brain networks due to regional volume differences in individuals. This motivates further investigation using approaches such as uniform seed size [7]. We presume that seed-based network analysis using the Modified-UBNIN holds promise for brain printing and biomarker discovery.

We once again appreciate the in-depth analysis of the UBNIN algorithm by Kelly et al.

**Author Contributions:** C.N.G. proposed the Modified-UBNIN to T.S. Then, the entire framework was built by T.S., M.A. and C.N.G. Data were provided by J.S. The manuscript was written by T.S., M.A. and C.N.G. The entire algorithm was coded by T.S. All authors have read and agreed to the published version of the manuscript.

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**Data Availability Statement:** The imaging and clinical data were collected from the National Institute of Mental Health and Neurosciences and may be provided upon approval as per Institute norms. The code developed for this work is available at our GitHub link below: https://github.com/NeuralLabIITGuwahati/Modified_UBNIN (accessed on 23 April 2024).

**Conflicts of Interest:** The authors declare no conflicts of interest.

## Appendix A

Minimum $UBNIN_T$ values from PD patients:

15360.000000000000000054188109290694681711540712349210283763615674543563352373044
540314108307985417491542032568424089945443628662866518209823592963211798055392 41
816286644066050002534601463189793536886562123148720978981963923225948578871873 57
906205374391073973233202698539587088993020644214333790700586144865839961061452 27
420852012700010002100292513335806451716586467312577373430032405405709877243052 22
317200146347124946039351530997460755117385076199567467690991306040700799642154 20
941391633447668937034943820696634960818229929741868486861118096851336023673250 67
951311474572261149742768387215023684837157623923840284894818543966267758303940 57
913616873609279398702479773602672559580207246500520927699473067664304142414169 33
141639974951867916474375461060828401020753774878489082866088587037836114464191 76
636876164494608780440495921331760578235732326495031020115232033649544357473581 77
270537055313439096642907456209101003273264236879571869160490505832564057515787 13
583560892230456949724746278646226468761639731275448798159969213526474173150659 02
620930914513062406797466111827341205712147583680713979575850121725871100442120 55
080923249110367086772223160345373592252143963060845624753653721674695706834110 03
164262003251969560504156866577281505919206060242797802543646624816081297610447 42
783175233251003138002420489476381931661623221427457494579818808502891866628524 24
004335553552461094260988098065710801935378196924161852693110927495120911058885 77
5249502770450904520771473471540957689285278320 3125

Maximum $UBNIN_T$ values from PD patients:

17768936615460608.00000000000000005416100591659316334300983261723046811367424604 7
280012246408829546387199112184955047207358311040032881652515738147739248264000 91
318104479023481862364994556633011230571546960015934766029037716235417075190175 29
420617975224796152208383982994359753569031796902346444663995664641200439764829 47
470747761172799373795039801873375790989077193154066812849603900383032074286352 90
065170089591647724824578274477546706216326277846362106572598818061611528576767 72
234129890598596775506933145925757243037105178108696976227823141614143484428045 77
977709795772373661272709254950516276552569103975328461295681242171432770079334 45
113142247259259090320570769098459135482634903731868112032654297865955616350055 62
061161698882326269351996847832767089766231328509539831035794998250623271811475 71
115635842163292709653678494294780894132133914309925621792983219752418811187857 67
276079852893050670095004215607765227620343663381002386068708749687819075355892 80
528302144964310086828009392488491104566330753527309724849029397191260712224229 85
387645315496839366686460619628411359764384007002617434368899768341319239553971 31
391840358587786184161151890529987253733378453918762644053229097930212979953205 33
176368670476188112221117637113389559696014726822438016498650838593327937934420 46
159041328689969082192935751992757608234116541780621956554991878126742133041030 13

4315361160817588799793546796130310603111565449829496126136440279267066968033352320764501742699243845742540504062390027684159576892852783203125

Minimum $UBNIN_T$ values from HC subjects:

12288.00000000000000054106795756270099824708156665866678597694453410061297132624468683434161970758629330185394426308045619802420004248780802617018084752258162368433073792884229621380081496543486157186728682507166150568632830866725370597355265509904749165711576438772020481799046492330113804477286514038126385698520210733348984936184815040083389673855326389015731931104410351369328894800511297409077876533450266016123245178647509464388162135194497190675383710986941299803441486640366201632425993916806853418055946306080584093002338298079971059566593125943777436993128446445737433699791444185162906106960140354047162921428296783597723492048459322004385870464606519289804044340284791109698243417771728595570889590502117662236078876410334679382535179925940813393002493000738210700402412238114412949300577779516563664592844549752948794491973298518914959150589150296327405663950565338386879568039799006767032761461373877501834403693081989412719520292905170721215178211744528858078484546412766455356135229784300560789002694130277550147970006179607373409563528598723800486895371628480529919868767750051368641576616974223375285256390486648379391778371720983853140457178140621259492744976815135775299924882093025707974917588313655995565749058790499302783581027523477051608226980300163344906265800997559890240179937417449242215015269855846254530571454746870881691588811013837177508838039476773136522454601722863201204365684245744676993071826385923573864451395672159339511608777684159576892852783203125

Maximum $UBNIN_T$ values from HC subjects:

17733751438064640.00000000000000054120348257576774496878925860742690765029916703066340407452168187419647341853151022767251464361357852396515113619741971631739794261206800703097794654538420886038233144144286873629854620833748683176513559142616774721867226550682213477792136035263694200097826678126465584507670723172624556991649365343609563839284715090638240407876142956237493780843015828676310143203703414335704100394239697698511895748326074473836296855050382508788033335734791089438321692458621634333649081591932277475205230436096070859818209011886874063829777814864422668774840504207434071549548434115607434283204876578563529885495216805998967980040828964324526181816720890552574459273339635394349653383895858410799147332543673426103202917476430439488511646880868440858965058957946868089285706907922003110407520811710497690370530695471826049662278424543823736533069781739853650264740713108383169738217576708839978370875687864788661310146031818995882427901525058541074884126813546100133209531239087433555966209647711464439339681368621344570557758221028631908679037726417030238316439229699365945970521195595419954011898173934670370722816273015032596918763552026748467672049662756200636645287155801001498491899469597186790061423863637172843987288280388884948994720576010921443955946036876236310381801406949849713390584554364916004622835090941625601112386421032464971225354016229270333487922002636106815454953416655833555156060961350522258906620627478668493799273016275908076977430027909576892852783203125

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