RAMSEY’S THEORY MEETS THE HUMAN BRAIN CONNECTOME

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ABSTRACT

Ramsey’s theory (RAM) from combinatorics and network theory goes looking for regularities and repeated patterns inside structures equipped with nodes and edges. RAM represents the outcome of a dual methodological commitment: by one side a top-down approach evaluates the possible arrangement of specific subgraphs when the number of graph’s vertices is already known, by another side a bottom-up approach calculates the possible number of graph’s vertices when the arrangement of specific subgraphs is already known. Since natural neural networks are often represented in terms of graphs, we propose to use RAM for the analytical and computational assessment of the human brain connectome, i.e., the distinctive anatomical/functional structure provided with vertices and edges at different coarse-grained scales. We retrospectively examined the literature regarding graph theory in neuroscience, looking for hints that might be related to the RAM framework. At first, we establish that the peculiar network required by RAM, i.e., a graph characterized by every vertex connected with all the others, does exist inside the human brain connectome. Then, we argue that the RAM approach to nervous networks might be able to trace unexpected functional interactions and unexplored motifs shared between different cortical and subcortical subareas. Furthermore, we describe how remarkable RAM outcomes, such as the Ramsey’s theorem and the Ramsey’s number, might contribute to quantify novel properties of neuronal networks and uncover still unknown anatomical connexions.

Keywords: Computer Science, Machine Learning, extremal set theory; Turán's theorem, Ramsey’s theorem.

Below is the unedited draft of the article that has been accepted for publication © 2022 Neural Processing Letters.

INTRODUCTION

Graphs are discrete mathematical structures equipped with vertices joined by edges (Wilson 2010; Diestel 2018). They represent the common, general manifolds subtending the phase spaces of our logical, mathematical, physical, chemical, biophysical and biological worlds. The Ramsey’s theory (RAM) from combinatorics and network theory examines the intrinsic mathematical features endowed in graphs (Graham et al., 1990). Suggesting the general conditions for the existence of orderly substructures with regular properties, RAM advocates that large sets of elements (say numbers, points, planes, objects, image tessellations and so on) unavoidably contain repetitive geometric patterns (Bondy and Murty, 2008). Problems in RAM are usually tackled in terms of edge-coloured graphs such as, e.g., no matter how you n-color the edges, when the graph is large enough you will always find certain subgraphs with monochromatic edge labelling. A typical example of RAM is the problem of friends and strangers, which proves that at a gathering of any six people some three of them are either mutual acquaintances or complete strangers to each other.

RAM probes the emergence of the order that arises when different kinds of structures grow large enough. Hence, it has been profitably used in far-flung scientific fields. Interesting applications include game theory, decision making, metamathematics, communications, approximation algorithms, harmonic analysis, ergodic theory, convex and computational geometry, probabilistic method versus constructions, information retrieval in computer science, dual source codes, MaxSAT NP-hard computation problems, lower bound arguments for Parallel Random-Access Machine and for Boolean function computation (Roberts 1984; Rosta, 2004; Molnár et al., 2018).

Here we suggest using RAM for the assessment of the anatomical and functional neural network known as the human brain connectome. The cortical and subcortical areas of the central nervous system form a hierarchy characterized by community structures of densely interconnected brain subareas, each one standing for a graph vertex (Sporns et al., 2005; Reese et al., 2012; Peters et al., 2017). These networks can be described at different coarse-grained scales, from single neurons to neuronal populations and nervous tissue’s macroscale, corresponding to the various levels of spatial
resolution of the currently available imaging techniques. Even though the nervous networks’ graphs are often too large to be manually analysed, advanced methods such as graph database and analysis libraries have been combined to search for/identify remarkable subgraph patterns and motifs inside the ever-increasing amount of connectomics data sets (Matelsky et al., 2021). We will proceed as follows. At first, we will provide a gentle introduction to RAM and its theorems. Then, we will retrospectively go through the literature to ascertain whether RAM could be used to look for unknown, regular substructures hidden in the human connectome.

MATERIALS AND METHODS

By an operational standpoint, the aim of Ramsey’s theory is to answer to one of the two following reversed questions:

1) Given a certain graph with n vertices, do subgraphs with specific features exist? In this case, researchers look for the unknown number of potential subgraphs encompassed in graphs with already known numbers n of vertices.

2) Given a subgraph with specific features, which is the number n of vertices that a certain graph must have to encompass such subgraph? In this reverse case, researchers look for the required graphs with sufficiently many edges to contain already known structures as subgraphs. RAM calculates how many elements of a certain structure must be counted to guarantee the existence of a certain property.

Here we focus on the Ramsey’s theorem (RT) and the Ramsey’s number, two of the most distinguished RAM outcomes. RT refers just to complete graphs Kₙ, i.e., graphs in which every pair of distinct vertices n is connected by a unique undirected edge. To provide an example, Figure 1A illustrates a Kₐ complete graph. RT states that a complete monochromatic sub graph will always be found in any edge color labelling of a large enough complete graph (Graham and Rothschild, 1971). To provide an example, let the edges of Kₐ be coloured with two colours, e.g., black and grey, representing two different features (Figure 1B). If two vertexes are connected by, say, a black edge, this means that they both display the black feature. According to RT, no matter how you colour with black or grey the edges of Kₐ, you cannot avoid the existence of:

   a) either a triangle whose three sides are all black,
   b) or a triangle whose three sides are all grey (Figure 1B).

The conclusion is straightforward: whatever colours are used, there will always be at least one monochromatic figure (that is, a figure with all the edges of the same color). Since n vertices correspond to about n² edges, there are many ways to color the edges.

Therefore, for each pair of positive integers k and l there exists an integer R(k,l) (known as the Ramsey number) such that any graph with R(k,l) nodes contains a clique with at least k nodes or an independent set with at least l nodes. The general formula of the Ramsey’s number reads:

\[ R(k,l) = V \]

Where k stands for the number of sides of the figure coloured with one color, l stands for the number of sides of the figure coloured with another color, R(k,l) is an integer depending on both k and l, and V stands for the number of vertexes (Allen 2008). The two terms \((k,l)\) suggest that we are using a 2-coloring of the edges. In other words, the Ramsey’s number is the minimum number of vertices \(V = R(k,l)\) such that all undirected simple graphs of order v contain a clique of order k or an independent set of order l. RT states that such a number exists for all \(k\) and \(l\). Another statement of RT sounds as follows: for integers \(k,l \geq 2\), there exists at least a positive integer \(R(k,l)\) such that no matter how the complete graph \(K_{R(k,l)}\) is two-colored, it will contain a subgraph \(K_k\) or a subgraph \(K_l\).

The above-mentioned \(K_6\) example is conventionally described by the formula:

\[ R(3,3) = 6 \]

The formula reads as follows: if you have a complete graph with the edges forming either a tree-sided black figure or a tree-sided grey figure, the complete graph must display at least 6 vertexes. In case of a subset of at least three completely uniform edges, RT guarantees that such subset is provided by a hexagonal graph. We will see in the sequel that the coloured graphs’ black colors may stand for biophysical features such as, e.g., the spiking cerebral areas, while the grey colors for the non-spiking cerebral areas.

RT copes with the existence of monochromatic subsets characterized by connected edges of just one colour. Nevertheless, when the number \(n\) of the complete graphs’ vertices increases, the number of possible colorings becomes very intricate. The Ramsey’s numbers for the smallest values of \(K_n\) are known: for example, \(R(3,3) = 6\) and \(R(4,4) = 18\). Yet, when considering the huge available number of subgraphs with different colors, the Ramsey’s number becomes almost impossible to calculate (Ajtai et al., 1980). For higher \(K_n\), only approximate bounds of the Ramsey’s number are known (Angeltveit and McKay, 2017): for example, \(R(5,5)\) is only known to lie in the range 43–49 (Figure 1C), while
R(6,6)=102-165. It is worth mentioning that RT works also for multidimensional graphs (Hindman and Strauss, 1998). The example of the hypercube is provided in Figure 1D. In this case, RT allows us to answer to the following questions:

a) What is the smallest number of dimensions of a $n$-dimensional hypercube, in which all vertex pairs form lines that all are colored with one of two colors (say black or grey), such that there must exist a monochromatic complete graph of four coplanar vertices? The answer is four.

b) What is the smallest number of edges of a hypercube such that all the available colorings will contain a monochromatic $K^4$ with four coplanar vertices? The answer is eight.

Apart from RT, RAM includes other useful theorems that could be helpful to improve the graph theoretical analysis of the human brain connectome. A subfield of RAM, i.e., the extremal graph theory (EGT), describes graphs with sufficiently many edges to encompass the required structures as intermediate-sized subgraphs (Bondy 1971; Szemerédi 1975; Bollobás 2004). Interesting possibilities could be given by manifold, intriguing EGT theorems (Motzkin and Straus, 1965; Bárány and Valtr, 1998; Büyükçolak et al., 2019). We will focus here just on one of them, i.e., the Dirac’s theorem, which states that very $n$-vertex simple graph all of whose vertices have degree at least $n/2$ has a Hamilton cycle, i.e., is a path that visits each vertex exactly once.

**Ramsey’s theorem and the mathematics of the human brain connectome.** In the last decades, graph theoretical analysis was used to generate different kinds of graphs, such as the widely-diffused neural, convolutional and recurrent networks (Zhou et al., 2020). Concerning the neuroscientific field, the human brain connectome’s networks have been mapped through a vast array of different techniques. Brain connectivity patterns (both anatomical and functional) are classified in terms of statistical dependencies (functional connectivity) or of causal interactions (effective connectivity) among various neural units, allowing neuroscientists and medical doctors to make inferences regarding human cognition, behaviour and nervous disorders (Farahani et al., 2019). Anatomical human brain connectome’s graphs equipped with up to 1015 vertices and several thousand edges have been attained (Fellner et al., 2020b). Starting from the Human Connectome Project’s freely available data relative to 413 healthy human young adults (http://www.humanconnectome.org/documentation/S500), Fellner et al. (2020b) evaluated the frequent graph edges and subgraphs extracted from hundreds of high-quality MR images. The frequent edges were computed through the Budapest Reference Connectome Server (Szalkai et al., 2017), in which the edge frequency threshold $k\%$ can be selected. The resulting connectome contains only the edges present in at least $k\%$ of the subjects. In literature, every node roughly corresponds to an anatomically labelled area or subarea of the gray matter, while every edge corresponds to the axonal fibers connecting different areas or subareas. Still, the complete graphs’ vertices do not refer to the neuronal microscopic level, rather represent larger Region of Interests that are densely connected to each other.

We propose to use the RT framework for the assessment of neuronal networks, in order to improve our knowledge of the connectivity among different brain subareas. To tackle our goal, we went retrospectively through the literature, looking for tacit remarks pointing towards the occurrence of RAM structures in the human brain connectome. We aimed to look for the occurrence in the human brain connectome’s datasets provided by Fellner et al. (2020b) of the complete subgraphs (all-to-all connected brain regions) required by RT.
**Figures 1A-B.** Ramsey’s theorem in case of Ramsey’s number $R(3,3) = 6$. **1A:** a complete $K_6$ graph, geometrically forming the edge set of an exahedron with 15 edges. **1B:** every pair of vertices is connected with a black or grey edge. No matter how the black or grey lines are arranged, there will always be a triangle that is either black, or grey. One of the many available black triangles is portrayed.

**Figure 1C.** Ramsey’s theorem in case of Ramsey’s number $R(5, 5)=43$. The best coloring of the complete graph $K_{43}$ contains monochromatic figures (the black pentagon in Figure) sitting on 5 nodes. Modified from: Molnár et al. (2018).

**Figure 1D.** Ramsey’s theorem in the case of a complete three-dimensional graph with 8 edges, i.e., a hypercube. The Figure shows that the hypercube can contain, among countless others, a black rectangle, i.e., a monochromatic $K_4$ with four coplanar vertices. Modified from: https://sites.google.com/site/pointlesslargenumberstuff/home/2/grahamsnumber
RESULTS

Do complete graphs exist in the human connectome? Our RAM approach to real nervous networks requires the existence in the human brain connectome of rather peculiar graphs, i.e., graphs that are technically referred as complete. Therefore, the question is: does the human brain connectome contain graphs in which every pair of distinct brain subareas is connected by a unique edge? Examining the published data, we found that the answer is affirmative, thanks to the works of You et al. (2020) and Fellner et al. (2020a; 2020b). You et al. (2020), exploring the design space of various relational graphs based on average path length and clustering coefficient, describe the features of complete graphs of fully connected layers. Fellner et al. (2020b) provided an effort to map the complete graphs of the human brain networks. Assessing the human brain graphs of 413 subjects from the dataset of the Human Connectome Project, each one consisting of 463 nodes, they listed the complete subgraphs present in at least the 80% of the available samples. Figure 2A provides an example of a $K_6$ subgraph detected by graph theoretical analysis. It is noteworthy that many of the complete subgraphs are located in the striatum and that just a few of them display nodes in both the hemispheres. Further, the right hippocampus and the right amygdala occur in much more complete subgraphs than the left ones, while the left thalamus-proper, the left putamen and the left pallidum occur in much more complete subgraphs than the right ones (Fellner et al., 2020b).

For our RAM purposes, the required nervous subgraphs must be equipped with a number of vertices $\geq 6$. Fellner et al. (2020b) found forty-eight $K_6$ and two $K_7$ complete subgraphs endowed in about 80% of the assessed connectomes, mostly (forty-two) located in the left hemisphere. Below are a few examples of the $K_6$ subgraphs detected in the human central nervous system:

- a) Left-Putamen, lh.lateralorbitofrontal_6, lh.lateralorbitofrontal_7, lh.parstriangularis_3, lh.rostralmiddlefrontal_12, lh.rostralmiddlefrontal_9. This subgraph is illustrated in Figure 2B.
- b) Left-Putamen, lh.lateralorbitofrontal_4, lh.lateralorbitofrontal_6, lh.parstriangularis_3, lh.rostralmiddlefrontal_12, lh.rostralmiddlefrontal_9
- c) Right-Accumbens-area, Right-Caudate, Right-Hippocampus, Right-Pallidum, Right-Putamen, Right-Thalamus-Proper
- d) Right-Amygdala, Right-Caudate, Right-Hippocampus, Right-Pallidum, Right-Putamen, Right-Thalamus-Proper
- e) Left-Caudate, Left-Putamen, Left-Thalamus-Proper, lh.precentral_11, lh.precentral_4, lh.precentral_7
- f) Left-Caudate, Left-Putamen, lh.caudalanteriorcingulate_1, lh.caudalanteriorcingulate_2, lh.rostralanteriorcingulate_1, lh.rostralanteriorcingulate_2

Just two $K_7$ complete subgraphs have been found in the human central nervous system, both located in the left hemisphere:

- a) The first one connects the left putamen with six vertices in the left frontal lobe. The seven vertices correspond to the following anatomical zones: Left-Putamen, lh.lateralorbitofrontal_4, lh.lateralorbitofrontal_6, lh.lateralorbitofrontal_7, lh.parstriangularis_3, lh.rostralmiddlefrontal_12, lh.rostralmiddlefrontal_9
- b) the second one connects the left caudate and the left putamen to five left frontal areas. The seven vertices correspond to the following anatomical zones: Left-Caudate, Left-Putamen, lh.lateralorbitofrontal_7, lh.medialorbitofrontal_2, (lh.rostralanteriorcingulate_1, lh.rostralmiddlefrontal_12, lh.rostralmiddlefrontal_9

RAM in neuroscience: operational issues. In the previous paragraph, going through the published literature, we confirmed the existence in the human brain connectome of the complete subgraphs equipped with at least six vertices required by RT. The next step is to illustrate some of the RAM procedures that could be used to assess neuronal networks. To provide an example, Figure 2B illustrates one of the $K_6$ complete subgraphs endowed in the human connectome, in which every vertex stands for a different anatomical brain subarea (Fellner et al., 2020b). We propose to use complete subgraphs to investigate the dynamics of activated and deactivated brain areas. In a neuroscientific context, the coloured graphs’ black color can be replaced by cerebral areas that are currently active, while the coloured graphs’ grey color can be replaced by cerebral areas that are currently inactive. Therefore, each vertex can be represented either as a black dot standing for an activated subarea, or a grey dot standing for a deactivated subarea. When an edge links two vertexes that simultaneously display the same color, the edge is depicted with the same color. In Figure 2B, for example, three subareas are simultaneously activated and can be therefore portrayed as a black triangle with black edges. RT suggests that, in each of the forty-eight $K_6$ complete subgraphs endowed in the human brain connectome, there must always be at least three brain subareas that are simultaneously either activated or deactivated.

Apart from the opportunity to predict the simultaneous activation of brain subareas (i.e., the vertices of complete graphs) connected by neural paths (i.e., the edges of complete graphs), RT also suggests other useful applications. The
Ramsey’s number predicts the features and the arrangement of the complete networks potentially underlying the experimentally detected activated subareas. To make an example, if the simultaneous activation of four subareas is identified in which every pair of vertices is connected by a unique edge, RT dictates that the ensuing quadrangle must be encompassed inside a complete graph equipped with at least 18 vertices. This means that at least 18 brain subareas must be involved. This bottom-up approach paves the way to the possibility to discover unexplored connexions among hidden brain subareas that are simultaneously activated (or deactivated).

To provide an example of the countless possibilities of the extremal graph theory in the study of nervous connectomics, we will examine a viable application of the Dirac’s theorem. Contrary to complete graphs, simple graphs (Figure 2C) do not contain graph loops and multiple edges (Bronshtein and Semendyayev 2004; Christofides et al., 2012). Since the simple graph displays vertices with degree at least \( n/2 \), the Dirac’s theorem dictates that a path crossing each vertex exactly once must unavoidably occur (Figure 2D). This means that the existence of Hamiltonian paths is mandatory inside the substructures endowed in the human brain connectome. In turn, a path that crosses each vertex exactly once is not allowed when the macro-structure of the whole connectome is assessed in terms of a huge, single and simple graph. In this case, the simple graph’s requirements of the Dirac’s theorem are not guaranteed (Figure 2E). This means that quick paths visiting just once a series of brain subareas are allowed, while quick paths visiting just once all the brain areas are not allowed. This suggests that a nervous path must be redundant to cross the whole brain, being required to cross a single node at least \( \geq 2 \) times.

In conclusion, RAM suggests a twofold novel approach to the study of the brain connections:
1) to start from a known complete network and look for the brain subareas that must necessarily be simultaneously activated.
2) to start from the simultaneously activated brain subareas and look for the subtending, unknown complete network.
**Figure 2A.** A complete subgraph with four vertices endowed in the human connectome. This $K_4$ graph connects four anatomical zones, termed: Left-Caudate, Left-Pallidum, Left-Putamen and Left-Thalamus-Proper. Modified from Fellner et al. (2020b).

**Figure 2B.** In this $K_6$ graph, every vertex stands for one of the anatomical subareas of the connectome described by Fellner et al. (2020b). Each vertex is illustrated as a black dot (an activated brain subarea) or...
a grey dot (a deactivated brain subarea). When an edge links two vertexes with the same colour, the edge will be of the same colour. The figure depicts the occurrence of a black triangle with black edges in which three brain subareas are simultaneously activated.

**Figures 2C-E.** Dirac’s theorem and the human brain connectome. Given a simple graph with 6 vertices (Figure 2C), a path visiting each vertex exactly once (grey line) is allowed if all the vertices have a degree at least \( n/2 \) (Figure 2D). In the case of Figure 2C, the degree is at least three. Figure 2E: in turn, the Dirac’s theorem does not hold when the whole connectome is assessed as a single graph. In this simplified sketch of the bilateral human connectome (van den Heuvel and Sporns, 2011), every vertex of this 14-vertexes graph does not display more than 6 edges: this means that a path visiting every vertex exactly once is forbidden by the Dirac’s theorem.

**CONCLUSIONS**

We suggest that a Ramsey’s theory-framed narrative of human brain’s connectome dynamics could be able to provide alternative approaches in respect to graph theoretical analysis of neuronal networks. One of the widely used theorem from RAM is the Ramsey’s theorem (RT). RT descriptions are usually tackled in terms of edge-coloured complete graphs, such that the theorem guarantees a monochromatic coloring in any two-edge-coloured vertex complete graph. Concerning neuroscience, we suggested that, given six brain areas arranged in a complete graph, three of them must be simultaneously activated or deactivated. Graph theory is becoming a widely diffused tool to cope with the current availability of large amounts of neuroscientific data. Yet, brain network reconstruction with complex network representation involves biased theoretical assumptions that affect networks reconstruction and properties (Korhonen et al., 2021). Some authors consider neurodata as the vectors of amplitudes of a multivariate signal, while others compare the similarity matrix computed between signals from different brain regions or look for features that are invariant under continuous deformations (Billings et al., 2021). To assess nervous dynamics and describe the intrinsic taxonomy of neural architectures, several studies used different types of networks (Khan et al., 2020). For example, topological data analysis delivers tools that describe the shape of data in terms of holes or cavities (Sizemore et al., 2018). This successful method, based on the notion of simplicial complexes, provides results robust under continuous data deformation (Salnikov et al. 2018). Of course, every one of the available methods comes with pros and cons, but we are not going to discuss them. What interest us is that RT requires the existence of distinctive complete graphs endowed in the human brain connectome, such that every pair of distinct brain subareas must be connected by a unique undirected edge. These peculiar graphs, although not frequent, do exist in the human brain connectome (Fellner et al., 2020b). Complete graphs are well represented in real biological neural networks, in particular in the structures displaying densely connected “rich club property” (van den Heuvel and Sporns 2011; Ball et al., 2014). As stated above, complete graphs provide us with the operational opportunity to treat neuronal networks in terms of RT. Another invaluable advantage of complete graphs is that no anatomical contiguity is required among the brain subareas located in every vertex. To provide an example, take the two vertices that have been termed lh.rostralmiddlefrontal_9 and Left-Putamen in Figure 2B. The very configuration of the complete graph permits to move and locate the two above mentioned anatomical areas in whatsoever vertex, since every subarea must be adjacent to every other. This means that the brain subareas belonging to complete graphs must always display functional connectivity, even though they are anatomically far apart. Relatively straightforward networks are achieved that are more manageable and easier to build, compared with the usual networks that make up the human brain connectome.

As stated above, RT can be operationally used to solve two inverse questions. On one hand, in any graph in which all points are connected by either black lines or grey lines, a large subset of the graph that is either all black or all grey is guaranteed. On the other hand, every uniform subset (no matter how it is great) is unavoidably encompassed in a graph with a well-known minimum number of vertices.

RAM could be used also in neuroscientific disciplines different from connectomics (Laughlin 2013). Take, for example, the Holland’s hexagon model, widely used for the experimental evaluation of vocational interests (Holland, 1997). This model consists of a complete graph that incorporates six interrelated interest areas, each one standing for a vertex: Realistic, Investigative, Artistic, Social, Enterprising, and Conventional. A RAM approach suggests that at least three of these six features must be either present or absent in subjects undergoing MRI and voxel-based morphometry to investigate the psychometric relationships between vocational interests and abilities (see, e.g., Schroeder et al., 2012). Another feasible possibility is to correlate RT with the Boolean logic. In our example of Figure 2B, the activation/deactivation of brain subareas might correspond to the Boolean functions YES/NO. This means that, with the proper adjustments, RAM could be also used to assess complete graph-like Boolean networks. By an epistemological standpoint, a RAM approach to neuronal issues suggests that, leaving apart specifically committed physical/biological explanations, the simultaneous activation of connectome subareas (usually detected
through pairwise comparison techniques) might stand for a nervous mechanism exclusively depending on the inherent graph arrangement.

DECLARATION OF INTEREST

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The Author does not have any known or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, their work.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

This research does not contain any studies with human participants or animals performed by the Author.

The Author had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The Author performed: study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, statistical analysis, obtained funding, administrative, technical, and material support, study supervision.

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