OPTIMIZERS 2050

Avi Peled Debbie Brand

ISBN: 1-894936-56-6
9781894936569
SAGA BOOKS
Sagabooks.net

Part I: Investigation

Chapter 1

Dan Moor drove into the parking lot at University Hospital and pulled into an empty space facing the building. He switched off the engine and sat behind the wheel, staring at the psychiatric wing. Of average height and build, Dan's sandy colored hair bordered on unruly. He ran his fingers through it now, feelings of anticipation and apprehension making his stomach churn.

The year is 2050 and Dan has just graduated from the Optimizers Pre-residency Program for psychiatry. The Optimizers program was developed some three decades ago as a special training program for those wanting to become psychiatrists. Only the top students can compete for the optimizers program after graduating from medical school.

The scientific leap forward in brain research over the last four decades has put psychiatry in the forefront of medical disciplines. Brain medicine involves mastering advanced knowledge from mathematics and physics of complex systems, so it was inevitable that a special training program would be developed to keep pace with advances in the field.

Dan reached into the back seat and picked up his briefcase. In an effort to calm himself as he left the car, he focused on the elements that constituted the basic sciences of the four-year pre-psychiatry program—neural computation, neuroscience and computer-generated signal analysis of imaging devices. Non-linear higher-level mathematics had become indispensable in psychiatry.

Unlike other medical doctors, psychiatrists are now called optimizers. This is partly because they were required to graduate from the optimizers program but more because curing mental disorders involves optimizing brain functions, especially those functions of higher levels.

Approaching the psychiatric department, Dan could see Dr O’Connor through the glass doors. Tall, dark and immaculate with piercing grey eyes, he was an imposing figure. He was also Dan’s appointed supervisor for the first twelve months of his residency. Beside him was Professor Krauss, whose white hair and twinkling eyes made him appear more like a benevolent grandfather than a professor with more than forty years experience in psychiatry. Although retired, he still visited the department regularly, offering his wealth of experience in clinical supervision. Professor Krauss had heard lectures from great psychiatry authors dating back to the pre-optimizers era, even before the introduction of Theoretical Psychiatry[1], having graduated from what was then called a biological psychiatry residency.

The professor’s presence reassured Dan and dispelled the last of his anxiety. After they exchanged greetings, Dr O’Connor informed him that he would receive his first patients soon. ‘In the meantime,’ advised Dr O’Connor, ‘you might like to go over your IVI procedures.’

Professor Krauss accompanied Dan to the staff lounge. There were a number of small offices adjoining the lounge and one had Dan’s name in the slot on the door. Dan put his briefcase away and rejoined the professor in the lounge, where they discussed the three basic phases for optimization in the treatment of mental disorders—Investigation, Validation and Intervention. They both looked up when Dr O’Connor appeared in the doorway.

‘Dr Moor, we will see three new admissions now,’ he said.

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[1] Peled 2004

Dan looked at the professor who nodded and said, ‘We will talk again.’

‘I look forward to it,’ smiled Dan and walked briskly to the ward with Dr O’Connor.

‘They were admitted last night,’ said the doctor as he increased his speed. ‘You will be able to start the Investigation phase for these patients right away.’

Chapter 2

On the way to the ward, Dan vividly recalled one of the early lectures from the Optimizers pre-residency program. He could almost hear the speaker's voice, 'Investigation is a term dating back some four decades to the year 2008. It refers to the initial evaluations of psychiatric patients using a complex system approach. The approach was considerably influenced by an initially anonymous publication[1], which was probably the first systemized description of mental disorders as pure brain perturbations.

During that era, psychiatric care was based on a problematic descriptive diagnostic system. In this system, mental disorders were descriptive entities constructed purely from descriptions of patients' complaints and appearances. Checklists of signs and symptoms formed clinical entities of mental disorders. This diagnostic method was detailed and published periodically[2] but each new edition varied somewhat, based on new insights and considerations.

Those were difficult times, the high hopes that these entities would correlate with known causes or biological markers, as they were termed in those days, failed[3]. It was a time of frustration which led to the claim that, 'We are at the epicycle stage of psychiatry where astronomy was before Copernicus and biology before Darwin[4].' Even though effective medications were beginning to appear, no real insights as to how these medications worked had been provided and contradictions were not unusual. For example, depression and anxiety were distinct clinical

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[1] *Brain Dynamics and Mental Disorders,* Peled 2004
[2] *Diagnostic and Statistical Manual of Mental Disorders,* American Psychiatric Association
[3] Helmut 2003
[4] Allen Frances in Kendell and Jablensky 2003

entities but the medications that treated them effectively were of the same class.’

Entering the ward, Dan and Dr O’Connor stopped at the nurses’ station where Dr O’Connor picked up a clipboard containing papers and handed it to Dan.

‘We will discuss your Investigations after you have seen all three patients,’ Dr O’Connor said. Dan nodded as the doctor turned and strode back down the corridor.

Chapter 3

Dan ran his fingers through his hair and looked at the top sheet. Steve, 26 years old, had been brought to the emergency room late the day before, after he smashed the television set at home. His parents complained of his irrational behavior during the past three months, which had become unbearable in the last week. He had refused help and his condition worsened, resulting in this violent outburst. Dan read in the patient's history that this was not the first time Steve had suffered a psychotic episode.

Four years ago, Steve had attacked an old man on the street. In court, Steve said that the old man was not really an old man, he was an extraterrestrial sent to abduct him to a remote planet. The judge realized Steve needed psychiatric help and he was hospitalized. Steve was a law student at the time, under tremendous pressure, preparing for his bar exams. He had been taking amphetamines to help him stay awake to study and occasionally smoked marijuana to ease the stress typically experienced before exams.

Dan made a note to order the records from Steve's previous hospitalization, as it seemed that optimization had not been employed. This was not unusual. Optimization procedures are extremely expensive and are reserved for clear-cut cases. Often, it is only at the second or third hospitalization that optimization is implemented.

As Steve's first psychotic attack was short and resolved quickly with traditional medication, it was probably diagnosed as a temporary perturbation to brain organization, caused by psychoactive drugs. Now that Steve had suffered another episode, Dan thought that optimization should be considered seriously for Steve. It would be up to Dan to evaluate Steve and decide whether his brain suffered only a mild temporary perturbation or a more serious brain organization disturbance.

Dan entered the room and found Steve sitting at the head of the bed with his back against the wall. He seemed unaware of Dan's arrival, which gave Dan the opportunity to study him before starting the interview. Although it was obvious he had showered and was wearing clean pajamas, Steve looked rumpled and unkempt. His dark, wavy hair was damp and matted, his nails rough and dirty. He had not shaved for some time and there were food particles lodged in his beard.

Dan moved to the side of the bed and began his interview, although Steve would not look directly at him. Steve's speech was disordered, he jumped from one subject to the next without any logical connection and his responses were unrelated to the questions Dan asked. What he suffered from was once called loosening of associations. This was an indication of disrupted global organizations of the dynamic core.

Dan left Steve and stopped at the nurse's station. 'Would you contact Steve's parents and arrange a time for me to speak with them, please?' he requested.

'Steve's mother will be here in about twenty minutes,' answered the nurse. 'She was here earlier but had to leave and said she would return in an hour. I'll page you when she arrives.'

'Thank you,' said Dan and he headed back to the staff lounge for a cup of coffee and some contemplation.

Chapter 4

While making his drink, Dan heard footsteps and turned to see Professor Krauss enter the lounge. ‘Black with one sugar, thank you,’ he said with a smile.

Dan obliged, handing the cup to the professor and they sat down across from each other at the low table.

‘I’m glad you are here,’ said Dan. ‘On the way to the ward I remembered an early lecture about the history of Investigation. It must have been difficult in those days.’

‘Difficult, yes,’ replied Professor Krauss. ‘From the historical perspective it is even more frustrating that in those days, at the turn of the millennium, neuroscience had already achieved most of the basic knowledge needed for the Investigation phase of mental disorders. The discovery of a large number of insights towards brain organization[1] had already defined the concept of the dynamic core[2] as a functional cluster of neurons distributed to form high millisecond range integration, which also has a highly differentiated complexity.’

The professor leaned forward and looked at Dan as though expecting a response. ‘The dynamic core,’ said Dan, ‘is a functional cluster of neurons because the participating nerve cell groups are much more strongly interactive among themselves than with the rest of the brain. In addition, the high complexity of the dynamic core gives it the ability to choose its activity patterns from a very large repertoire in less than a second.’

This must have been the response Professor Krauss expected because he nodded his head slowly. ‘The basis for scientifically approaching brain organization was laid with the descriptions of neural complexity and matching complexity[3],’ stated the professor. ‘The mathematical

[1] Tononi et al. 1994, 1996; Tononi and Edelman 1998, 2000
[2] Edelman and Tononi 2000; Van Quyen 2000
[3] Tononi et al. 1994, 1996

concept of neural complexity, C_N[1], captures the important interplay between integration and segregation.' Again he looked pointedly at Dan, with a twinkle in his eyes.

Enjoying this testing of his knowledge and understanding, Dan could barely suppress a grin as he parried with, 'Integration is functional connectivity, meaning the nerve cell groups work together. Segregation is the functional specialization of distinct neural subsystems. This means that small groups of nerve cells within the cluster perform specific functions.'

'In systems whose components are either totally independent or totally dependent C_N is low,' challenged Professor Krauss.

'And in those systems,' countered Dan, 'whose components simultaneously show independence in small subsets and increasing dependence in subsets of increasing size C_N is high.'

Before the professor could speak, Dan added, 'If the activities of different neural groups tend to be statistically independent then they are functionally segregated. Conversely, if they show a high degree of statistical dependence, groups are functionally integrated.'

'Functional segregation within a neural system,' finished Professor Krauss, 'is expressed in terms of the relative statistical independence of small subsets of the system, while functional integration is expressed in terms of significant deviations from this statistical independence[2].'

Dan laughed openly. 'I think you won this round, Professor,' he said.

'You are a very worthy opponent, Dan. Now let me hear what you know about matching complexity.'

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[1] Tononi et al. 1996
[2] Tononi et al. 1994

‘When a neural system is receiving sensory input, a change in C_N is observed. Matching complexity, C_M, reflects this change[1]. Using computer simulations, it was shown that when the synaptic connectivity—the area of contact between nerve cells across which impulses pass—is randomly organized, C_M is low and the functional connectivity does not reflect the statistics of the sensory input. If the synaptic connectivity is modified, the functional connectivity is altered so that many intrinsic correlations, or contacts, are strongly activated by the input. When this happens, C_M increases.’ Dan thought for a moment and then continued. ‘Also, once a range of intrinsic correlations, which match the statistics of the sensory input, has been selected it becomes critical to the way in which the brain understands or classes individual stimuli.’

‘Well done, my young friend,’ said Professor Krauss.

The sound of Dan’s pager put an end to further discussion. ‘I have a meeting with a patient’s mother,’ he said, smoothing his hair. ‘Thank you for the stimulating conversation, Professor. No doubt we will meet up again.’

‘No doubt,’ echoed the professor, leaning back and clasping his fingers across his middle. Dan smiled and headed off to the nurses’ station in the ward.

[1] Tononi et al. 1996

When he arrived at the ward, a nurse said, ‘Steve’s mother is in consultation room two, around the corner to the right.’

‘Thank you,’ Dan replied cheerfully, still buoyed by his conversation with Professor Krauss.

The door to the consultation room was open and Dan could see Steve’s mother sitting at the table. Her concern was clearly visible on her face and in her posture. Dan’s mood sobered. He entered the room and after exchanging greetings and introductions he said, ‘Iris, I’ve read about the first psychotic episode Steve suffered. Tell me how Steve has been since then.’

‘Not good,’ Iris said tightly. ‘After Steve’s … since that other time, he hasn’t been the same. He couldn’t cope with his studies, he failed a few exams and dropped out of university.’ She gave a deep sigh and Dan waited patiently for her to continue. ‘A family friend gave him a job as a clerk in the insurance company he has. Steve’s job was a routine file updating process, which didn’t require much initiative or concentration or responsibility.’ Iris began wringing her hands. ‘He was just like any other boy, growing up. It must have been the pressure of university that caused the last episode but I don’t know what caused this one.’

Dan could see she was very close to tears. ‘The brain is a very complex structure,’ he said. ‘Instability can occur in all kinds of structures. External and internal disturbances can cause stable systems to become unstable but this instability does not necessarily happen just from some ordinary perturbation—disturbance. It has been said that it depends on the type and magnitude of the perturbation as well as the susceptibility of the system[1], which must be considered before the system is rendered

[1] Cambel 1993

unstable. Sometimes it takes more than one kind of disturbance for the system to transform into an unstable state. Others have spoken of the competition between stabilization through communication and instability through fluctuations. The outcome of that competition determines the threshold of stability[1].'

Iris was looking bewildered, so Dan explained further. 'In other words, the conditions must be ripe for upheaval to take place. In psychiatry, this is especially appropriate in describing the idea of acute reaction to stress and adjustment disorders.'

'The straw that broke the camel's back,' said Iris.

'Yes,' said Dan. 'That may be what finally allows the system to go haywire. That old saying reflects the idea of the trigger effect, where a small thing can cause a big reaction, bringing us back to the idea of instability as a behavior inherent to nonlinear systems.' Iris seemed satisfied with this explanation and looked slightly less troubled. 'What about Steve's personal life and habits? Have there been any changes?' Dan asked.

'Yes, a lot,' Iris nodded. 'He stopped seeing his friends and stopped going out with girls. Then he began staying closed in his room for hours on end. And he stopped looking after himself, not caring about his appearance.'

'That must have been worrying for you,' responded Dan, wondering if Steve's brain had suffered some higher-level organization degradation. 'We know that the higher-levels of brain hierarchy, found in areas of the brain and called the transmodal systems, are responsible for large-scale integrations[2], they combine lots of different information the brain receives. These same regions in the brain involve high-level functions such as concentration,

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[1] Prigogine and Stengers 1984
[2] Mesulam 1998

decision-making, categorization, abstraction and working memory functions. These functions are deficient in patients who were once called schizophrenics, especially those diagnosed as suffering from chronic and untreated schizophrenia. In the past, patients like Steve deteriorated to what was then called negative symptoms schizophrenia[1]. The symptoms of reduced thought, reduced willpower, reduced emotional response and blunt affect—which is reduced facial expression—correlate with social isolation and social as well as occupational deficiencies.'

'Things got worse,' Iris said, wiping her eyes. 'Steve started to hear things. At first he asked if someone had been visiting because he had heard voices, but nobody else had been in the house apart from me.'

'When did Steve first mention these voices?' queried Dan.

'About a month ago,' answered Iris, frowning. 'And I think it has been happening more frequently. Whenever he came out of his room, he would quickly turn his head at times as if he expected to see someone standing there. Other times Steve would cock his head as though he was listening to someone or something.' Iris looked questioningly at Dan.

'One more question,' Dan smiled. 'What happened last night, before you brought Steve here?'

'My husband and I were watching TV and Steve joined us. It was only about five minutes later that I noticed Steve's head sort of twitched around, then he glared at the TV and shouted for it to be quiet. I turned the volume down but that didn't help. He yelled "I said be quiet!" then he jumped up, grabbed an ornament and started to attack the TV, completely destroying it.' Fear and confusion clouded Iris's eyes. 'Dr Moor, what has happened to my son? Can you help him?'

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[1] Andreasen 1983

Dan's thoughts darted back to recall that hearing voices indicated brain global disintegrations, previously described by using a masked speech tracking task[1]. The results supported the hypothesis that the voices heard were counterfeit products of altered speech perception networks. Later[2], correlation analysis technique[3] was used to correlate brain activations associated with self-reports of auditory hallucinations in hallucinating patients. It was found that hallucinating participants demonstrated a network of cortical activations. The observed pattern of activation was consistent with models of auditory hallucinations as misremembered episodic memories of speech, and started to pave the way for what would become part of the validation phase used today.

'Through experiments,' Dan explained, 'we have discovered that the voices are actually memories of speech that are remembered incorrectly. I will schedule some tests for Steve and let you know what treatment he will receive. Try not to worry Iris, this is 2050—we're not in the dark ages anymore!' Dan gave her a big smile and was pleased to see her smile too, even if it was only a small one.

They left the room and Iris, looking slightly less distressed, went to visit Steve. Dan looked at his watch and decided to have an early lunch. He waved to the nurses on his way past their station and continued on to the cafeteria.

[1] Hoffman 1999
[2] Copolov et al. 2003
[3] [H_2(15)O] PET

Chapter 6

Winding his way through the hospital, Dan's thoughts returned to speech and past research that formed today's knowledge. Initial theories relating brain organization to speech activation emerged in the seventies of the previous century when speech was described as activation of semantic networks[1]. In the semantic network, concepts represent nodes or junctions and associations are represented by the connections of those nodes with other nodes and junctions.

Typically, the activation of concepts was regarded as spreading of activation. Once a concept in the semantic network is activated in thought or speech, it activates the relevant associated concepts linked to it by the pathways of the network. The idea of spreading of activation was generated and formulated mostly to explain and describe the results of priming and lexical decision tasks[2]. In these tasks, semantic activation was assessed through the identification and recognition of semantic stimuli. Their identification was made easier when the target stimulus was preceded, primed, by an associated concept. The activity created by the associated concept in the semantic networks activates the target concept to be identified and this enables the correct recognition of that target concept.

The principle parameters for assessing semantic organization with priming and lexical decision tasks involved reaction time and concept recognition. Other methods used in the assessment of semantic networks involved word generation fluency tasks[3] such as the animal fluency task. In these tasks, subjects were asked to spontaneously name animals as fast as they come to mind. Path analysis and categorization of the results were used to

[1] Collins and Quillian 1970
[2] Neely 1977
[3] Desse 1980

assess the organization of the semantic network, based on the assumptions that concepts in the network tend to categorize according to the associations among them.

As the science of neuronal modeling developed, models were also used to study semantic networks, with semantic networks implemented in parallel hardware[1]. By utilizing neuronal adaptation and a generalized neuronal activation function derived by a model[2], the dynamic control of semantic processes in a hierarchical associative memory was successfully modeled[3].

Later, a semantic network was implemented using a dynamic threshold attractor neural network[4]. In this model, elements simulated neurons and the connections between them simulated the synaptic connections of the neuronal tissue in the brain. That system also simulated the basic idea of system dynamics.

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[1] Hinton 1981
[2] Hodgkin-Huxley-type
[3] Cartling 1996
[4] Geva and Peled 2000

Dan had finally reached the cafeteria. He entered and while loading his food and drink onto a tray, he looked around for an empty table. He spotted one on the far side of the room and made his way towards it.

As he sat down, Dan could not help overhearing the conversation from the next table. He glanced briefly in that direction and saw a small group of students.

'It was prior to the turn of the millennium that the basic framework for understanding consciousness from a scientific point of view had already been provided[1],' said a female voice.

'Yes,' agreed a second voice, male. 'That was a theoretical workspace where global processes are formed from the interactions of many partial processes and the global formations in the workspace carry the global dominant message of conscious awareness[2].'

'Also,' this was the first voice again, 'a description of brain hierarchical organization had already been put forward[3] in a published paper[4].'

'True,' stated a third voice, also male. 'But although both descriptions nicely concurred, it wasn't until six years later that they were integrated for the first time[5].'

'It's the bit about partial processes that lost me,' admitted a fourth voice, female.

'Partial processes are specialized processes, each processing its information in an independent fashion,' said the first voice.

'They function in parallel,' continued the third voice. 'And if they're not involved in any global

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[1] Baars 1998
[2] Baars 1988
[3] Marcel Mesulam
[4] *From Sensation to Cognition*, Brain journal 1998
[5] Peled 2004

organization, they continue disconnected from other processes. Partial processes compete, cooperate and interact to gain access to and participate in global organizations.'

'Right,' said the second voice. 'Think of the global formation as a complex network of partial processes.'

'And in global formations,' added the third voice, 'there are internal consistencies and these form multiple constraints between the partial processes. When partial processes participate in the organization of a global process they are constrained by the activity patterns of the global formations.

'Partial processes,' continued the first voice, 'are fast, highly specialized and aimed at handling certain specific types of information. But they are limited in the extent of the information they can process and they lack the flexibility and adaptability required when many partial processes combine and cooperate. Global formations have both the complexity and the flexibility necessary for efficient and elaborate information processing.'

Dan was listening intently, finding it difficult to continue eating and not join in this discussion.

'So, combining these ideas,' the fourth voice spoke hesitantly, 'it is reasonable to consider that lower level partial processes in the nervous system interact to form higher-level neural global organizations.'

'Yes,' responded the third voice. 'According to one source[1], the lower-level processes are the unimodal systems interacting to form multimodal organizations. The higher-level processes are the transmodal systems that achieve the global organizations or workspace described as the dynamic core of distributed organization. These transmodal systems were described as appertaining to certain parts of the brain[2].'

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[1] Mesulam

[2] frontal cortex, hippocampal formations and certain parietal-temporal association cortex

‘The idea of internal consistency in global formations,’ said the second voice, ‘captures the basic notion of multiple constraint organization[1] in the sense that elements in the system are not free to act independently, since their activity is constrained by the activity of the elements connected to them. It is assumed that the dynamic activity of partial processes, or elements, demonstrates both hierarchical and multiple constraint organizations.’

‘Once the partial process becomes part of the global organization,’ explained the first voice, ‘it is interconnected with all the other processes and is broadcast globally. It contributes to, or influences, the global organization through its connections by exerting its output through these connections to the rest of the system.’

‘But,’ continued the second voice, ‘because it is a multiple constraint system, many other processes will constrain its activity.’

‘I see,’ said the fourth voice enthusiastically. ‘We can conclude that from the information processing point of view, there is a reciprocal relationship between the information delivered by partial processes and the global message.’

‘You’ve got it,’ the first voice said with a laugh. ‘The application of these early century ideas about brain organizations to psychiatry[2] had already provided the first intuitions about how systems and neural network models can be applied to the understanding of mental disorders. An innovative diagnostic language was based on these insights and prepared the foundation for what became the Investigation phase[3].’

‘Now that we’ve got that sorted out,’ said the second voice reluctantly, ‘the thing I’m not clear on is how

[1] Peled 1999
[2] Friston 1996, 1998; Hoffman 1986, 1997, 1999; Cohen, Cohen et al., 1996; Fuster 1995; Aakerlund and Hemmingsen 1998
[3] Peled 2004

a dynamic system works.' The others agreed that they too were unclear on the subject.

The voices fell silent and Dan continued eating until, 'Excuse me, Doctor?' he heard the first voice say.

Dan looked across with raised eyebrows, 'Yes?'

'We are not sure how a dynamic system works and wondered if you would care to explain?'

'Of course,' said Dan enthusiastically, abandoning the rest of his lunch and moving to join the students. Introductions revealed that the voices belonged to Rachel, Todd, Sonny and Claire, respectively.

Dan sat down and began his explanation. 'To picture how a dynamic system works, imagine a system formed from many elements. The arrangement of the elements in the system represents the states of the system and each distinct arrangement forms a different state. If the elements are arranged randomly, all the states in the system are similar to each other. If the elements of the system can form many distinct patterns of arrangements, then the system has many possible states.'

'What if the system can form only one type of arrangement?' asked Todd.

'Then the system is represented by one state only,' answered Dan. 'The space of a system is represented by all the possible states a system can assume. If the system changes over time, it is called a dynamic system. In a dynamic system, its arrangement changes from one point in time to the next.'

Dan looked around at the four faces and then continued. 'To visualize systems and their dynamics, a physicist[1] and a mathematician[2] devised the concept of state-space necessary for describing dynamics in physical systems[3]. A dynamic system is generally defined by a

[1] William Hamilton
[2] Karl Jacob
[3] Ditto and Pecora 1993

configuration-space consisting of a topological manifold. A point on the configuration-space represents the state of the system at a given instant. Each point is a combination pattern in the activity—the arrangement—of the elements. The configuration-space of the system is given by all of the possible states that the system is capable of assuming, all the possible combinations in the activity of the elements.'

'Isn't there something about scenery?' asked Rachel.

Dan tried not to smile too broadly. 'This configuration-space generates what is sometimes termed landscape. As the dynamic state of the system changes over time, the combinations in the activity of the elements change, which means the points on the space change. The dynamics of the system are described in terms of state-space as movement from one point to the next on the landscape, defining a trajectory—curve—on the configuration space.'

'What if the system prefers certain arrangements—states—over other states?' asked Claire, pushing her glasses back up her nose.

'In that case,' answered Dan, 'it will tend to be drawn or attracted to form these states. Once certain states are preferred by the system, they form attractors in the topological surface[1]. Peaks represent repellers, which are those states the system tends to avoid and basins represent attractors, which are those states the system tends to assume.'

'I remember reading how it was possible to simulate semantic concepts as attractor states—basins—embedded into the network by strengthening connections in a model[2],' said Sonny.

[1] Herz et al. 1991
[2] Geva and Peled 2000

‘Yes,’ said Dan. ‘And a psychologist stated that if neurons fire together the connections between them are strengthened[1]. Conversely, if the connections between neurons are strong these neurons will tend to fire together because they activate each other.’

‘So,’ said Todd, ‘sets of neurons firing together activate a state on the system space.’

Dan nodded. ‘By strengthening their connection, the system will tend to activate these neurons, which activates this state. The tendency of the system to activate a state, and dynamically moving to assume that state, is actually the formation of an attractor.’

‘The spreading of activation in the semantic network[2],’ said Sonny, ‘was simulated when the network state moved from one semantic concept to the next, or from one attractor state to another.’

Dan continued, ‘This was achieved by applying a dynamic threshold to all units that was gradually raised over time, causing the system to come out of the attractor and become ready to get into the next attractor, activating the next semantic concept. The concepts were associated through predetermined asymmetric connections that caused the network to move to a predetermined related concept.’

‘That model must have been very useful,’ mused Rachel.

‘It was,’ Dan affirmed. ‘It enabled simulation of disturbances of thought processes, especially the loosening of associations, poverty of thought and perseverations typical to thought disturbances in patients suffering from schizophrenia, as it was called back then. Being an approximation of neuronal systems in the brain, probably related to speech generation, the model offered a theoretical

[1] Hebb 1949

[2] Geva and Peled 2000

proposition as to how the brain may be disturbed in speech and thought disorders.'

Claire was frowning. 'Wasn't there some previous work with neural models?'

Dan smiled, 'A psychiatrist had pioneered similar work using a simple attractor neural network model[1]. Conclusions were that schizophrenia might relate to insufficient neuronal transmission among neurons in the cortex, defined then as over-pruning of synapses, and later models also suggested that a disconnection syndrome[2] could underlay certain schizophrenia signs and symptoms.'

'Thank you Dr Moor,' said Todd. 'We appreciate you clearing that up for us.'

'Anytime,' replied Dan.

He would have liked to stay in the cafeteria and continue talking with the students but he had to get his notes on Steve in order before his meeting with Dr O'Connor. 'Now I must leave,' he said, running his hand through his hair. Goodbyes were exchanged as Dan got up, then he worked his way to the staff lounge.

[1] Hoffman 1997
[2] Hoffman 1997; Friston 1998

Thinking about Steve's disordered speech on his way, Dan recalled that it was neural network models from the turn of the century that revealed the connection between speech disorganization and what was then called schizophrenia.

Current understanding of how this symptom reflects a disintegration of the dynamic core and global organizations in the brain, means that schizophrenia is now regarded simply as a disintegration or segregation of the dynamic core. The application of the system approach to speech and concept representations has been generalized to the neuronal organization of the brain[1]. Just as semantic concepts could be represented by interconnected elements in the network, neurons and their activations may also be represented as elements of the system. This simplification of neuronal network representation can suffice for insights on how the brain represents, activates and processes information. Even though simplified, these models were enough to gain basic insights to some of the formulations in the Investigation phase[2].

As well as insights regarding the neuronal basis of speech and thought in schizophrenia, the importance of assessment of the speech process for patients was also recognized and the speech of psychiatric patients began to be investigated and analyzed[3]. By applying a discourse analysis to schizophrenic and manic speech samples, it was found that the incoherence of manic speech was due to shifts from one coherent discourse—logical conversation—structure to another but the ability of schizophrenic speakers to construct any discourse structure was deficient.

Later, more sophisticated assessment began to reveal greater deviances of patient speech compared to

[1] Peled 2004
[2] Peled 2004
[3] Hoffman 1986

normal speech. Multidimensional scaling and clustering techniques were applied to analyze verbal fluency and other aspects of patients' speech[1]. Patients generated fewer words in fluency tasks and displayed more variable similarity groupings of words in other tasks. The results also showed little consistency within each individual patient. These results, even though not statistically conclusive, pointed towards the assumption that schizophrenia is associated with semantic disruptions.

Dan entered the staff lounge and absently poured himself a cup of coffee as his thoughts continued on speech analysis.

In the first decade of the century, information theory and mathematical applications were used to investigate speech analysis[2]. Deviations from normal speech were evaluated. Together with insights gained by neuronal network models, the deviations from normal speech could be mapped to state-space configurations that reconstructed the possible underlying disturbances to neuronal system organizations. Normal speech was evaluated by having a large sample of normal subjects repeat an essay read to them a few minutes earlier. These speech samples were used to establish statistical baselines of normal speech. Methods from information theory, especially by using hamming distance assessments—assessment of differences and deviations from normal baseline—gave mathematically validated and statistically significant counts and scoring to speech disorganization.

Later on[3], trajectory reconstructions of these deviations enabled mapping of different speech disturbances. For example, repetitions of subjects in speech—perseverations—activated the same points of the speech matrix map, forming a periodic trajectory.

[1] Elvevag and Storms 2003
[2] Future et al. 2006; Future and Future 2009
[3] Future et al. 2016

Disorganized speech with unrelated illogical jumps of loosening associations from one concept to another activated a discontinuous scattered trajectory compared to that of normal speech.

It was in the second and third decades of this century that an explosion of research in this direction[1] led to the development of the speech-cognition estimator system—SCE_{system}[2]. The SCE_{system} is an inexpensive indirect first-line tool to assess probable dynamic core disturbances. In effect, it replaced the neuropsychological testing of the past due to its additional capabilities, validity and reliability advantages. The SCEsystem is typically used in the Validation phase of the patient's condition.

Sitting down at his desk, Dan began putting his notes on Steve together. He had started the Investigation by evaluating Steve's brain organization in terms of global organizations, dynamic core[3] and global workspace[4] .

In the hypothesis section on the investigation form, Dan checked the box next to segregated dynamic core organization. Steve's hallucinations, in the form of annoying voices coming from the television, supported the disturbed dynamic-core hypothesis.

Dan completed his Investigation hypothesis based on Psychiatric Brain Profiling, PBP[5]. Using this formulation, the brain's mental disorders are evaluated as perturbations—disturbances—to the system of normal brain organization. It is an input-output formulation where inputs are perturbators, the causes of perturbations, and

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[1] Future et al. 2012; Future and Future 2015; Future et al. 2015; Future and Future 2016; Future et al. 2022; Future and Future 2025; Future et al. 2025; Future and Future 2029
[2] Future et al. 2042
[3] Edelman and Tononi 2000
[4] Baars 1988
[5] Peled 2004

outputs are the different patterns of perturbations caused to the system[1].

According to PBP, the hypothesis for Steve included reduced neural complexity with dynamic core segregation and accompanying hierarchical imbalance.

Steve scored positions 11 for trajectory jumps, 10 for modality disconnection and 6 for hierarchical insufficiency[2].

'I haven't seen you here before,' a cheerful female voice startled Dan.

'No. It's my first day,' he replied as looked up at the nurse standing in the doorway.

'I'm Helen,' she said with an amused expression on her face. 'Having a hard day?' she asked, looking pointedly at Dan's hair.

'Not really,' he replied, trying to smooth it down. 'I'm Dan Moor and I was just completing my Investigation notes on one of my patients.'

Helen entered the small office and looked at the name on the Investigation form. 'He's the fellow who smashed his TV. Interesting.'

Dan nodded. 'Steve's disordered speech and jumping from one concept to another indicates disconnected activations of state-space relevant to the various concepts.'

'Disordered speech is a reflection of loosening of associations, isn't it?' queried Helen, sitting down opposite Dan.

'That's right,' Dan agreed. 'Uncoordinated disconnected activations of states within the state-space configurations created by the cortical neuronal networks.'

'That explains the trajectory jumps,' said Helen. 'The modality disconnection?' she asked.

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[1] See Chart 1, Appendix
[2] See Chart 1, Appendix

‘This is based on hallucinations, which indicate that auditory modality processing is activated unconstrained or uncoordinated with the rest of the multimodal brain network.’

Helen frowned momentarily. ‘This is not a new discovery, is it?’

Dan shook his head. ‘The concept of disconnection within brain processing modalities was first formulated at the turn of the century[1] and was called functional disconnection syndrome.’

Helen looked at the form again. ‘Hierarchical insufficiency?’

‘This is based on collateral information showing that Steve’s social, occupational and motivational activity suffered impairment compared to pre-disorder conditions. There is a paper[2] that illustrates how the transmodal system, which is the highest level of brain organization[3], is responsible for integration of the total human experience into a meaningful action.’

Helen sat back and placed her chin in her hand. ‘How does that relate to motivation?’

‘At that time, motivation was hypothesized as an emergent property, arising from sensation-action integration occurring at the highest-level of transmodal brain organizations[4].’

‘Emergent property?’ asked Helen, leaning forward.

Dan thought back to his optimizer training regarding the mind-brain problem of explaining how neural networks are responsible for higher-mental functions such as feeling and thinking. It was crucial to understand the idea of emergent properties since they provide the

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[1] Friston 1996, 1998
[2] *From sensation to cognition*, Mesulam 1998
[3] Peled 2004
[4] Peled 2004

philosophical background for understanding how neuronal network activity is responsible for mental functions.

‘Emergent properties relate to the concept that the whole is more than the sum of its parts,’ Dan stated. ‘Put simply, the characteristics of the system as a whole are not explainable based on the characteristics of its isolated parts. Emergent properties are those components—parts—of a system that cannot be understood based only on the characteristics of the individual elements. Therefore, the characteristics of the system are greater than the sum of the attributes of the elements. When referring to mental functions as emergent properties from brain organization, it was stated[1] that neurons have never been demonstrated to possess psychological functions such as mood, awareness or intelligence. Such properties presumably emerge from the nervous system as a whole[2]. It is evident from brain research that microcircuits of neurons possess more properties than those that can be deduced from our understanding of the single neuron[3].’

‘So,’ summarized Helen, ‘The properties of activated brain regions are greater than the properties of microcircuits of neurons.’

‘Exactly,’ confirmed Dan. ‘Emergent properties originate from nonlinear systems.’

‘I know what they are,’ said Helen. ‘Nonlinear systems are those systems in which there are no one-to-one relations between input and output, so the activity of these systems cannot be described by linear equations.’

‘In linear systems,’ continued Dan, ‘the whole can be described by the sum of all parts. A change in the total system obeys an equation of the same form as the equation for the change in its elements. Linear systems cannot contain more properties than those of their components.’

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[1] Rosenblat 1962
[2] Rumelhart and McClelland, 1986
[3] King 1991

‘And nonlinear systems can?’ asked Helen.

‘Yes,’ said Dan. ‘Nonlinear systems may result in responses, or properties, that are greater than those predicted, thereby achieving emergent properties.’ Helen nodded slowly as Dan spoke. ‘When systems pass from random states to ordered formations, emergent properties arise in the system. These were not part of that system prior to organization, therefore, organization is at the basis of all emergent properties.’

‘Very interesting,’ said Helen, leaning back.

‘Nonlinear systems are often described by a sigmoid—curved—graph. The first portion of the graph can be viewed as a trigger-effect. This is where a small increase in input results in a large response in the output. The last portion of the sigmoid graph can be viewed as a saturation-effect, where the increase in input does not increase the output any further. Nonlinear systems can react abruptly to small changes—the trigger effect—or remain stable in spite of large perturbations—the saturation effect.’

‘Fascinating,’ said Helen. She looked at her watch. ‘Time to go. I will probably see you in the ward.’ She stood and was gone in a rapid whisper of rubber soles.

Coming back to Steve’s diagnosis, Dan thought therapy would require a multimodal reconstructive encephalography—MRE—and noted the details on the form. With Steve’s Investigation completed, Dan left for the Intensive Care Unit, ICU, where his next patient was being treated.

Chapter 9

When he arrived at ICU, a nurse directed him to Tim's bed. Tim was still unconscious and Dan looked at his magnetic resonance imaging—MRI—results. It was evident that Tim had suffered a severe blow to his forehead, which had not broken the skin but had caused bleeding in the membrane surrounding the brain and also in the brain itself. This was enough for Dan to know that even though it was an early phase for correcting brain damage, Tim needed the preliminary medication Bcl-2 up-regulator. This is part of the first-order brain plasticity inducers—BPIs—and is necessary to stop apoptosis—neuronal cell death—by blocking mitochondrial gene activation factors. These factors imitate and promote cell death[1].

Even though Tim's Investigation phase had just begun, it was necessary to implement portions of the third, Intervention, phase. Dan ordered the medication and approved Tim's transfer to the psychiatric department once he regained consciousness.

Dan went to the nurses' station and picked up the phone to inquire about his third patient. He was told that she was still in Pathology having blood and urine tests to check levels. As he hung up the phone, Dan's mid-section rumbled loudly, reminding him that he had not eaten all of his lunch. Dan decided to make his way back to the cafeteria.

'Dr Moor.'

Dan recognized Dr O'Connor's voice and turned to face him. 'Yes, Dr O'Connor?'

'What is the status of your Investigations?' the doctor demanded.

'I have completed Steve's Investigation,' said Dan consulting his notes. 'His therapy will require an MRE. I

[1] Charney and Manji 2004

have noted challenge coordinates MI[1]: 0.5, TOM[2]: 0.4, EI[3]: 0.1 and PS[4]: 0.1.'

Dr O'Connor gave a short nod. 'Your other patients?'

'Tim is still unconscious but I have started him on Bcl-2 up-regulator,' Dan replied.

'This procedure,' stated Dr O'Connor, 'is not consistent with the standard Investigation, Validation and Intervention framework of optimization.'

'No,' Dan supported his decision, 'but when Validation of Tim's brain damage is completed, the Intervention phase will also require in-depth BPI treatment.' Dr O'Connor said nothing. 'My third patient has not yet returned from Pathology.' Dan's stomach rumbled loudly again.

'Take your meal break,' said Dr O'Connor as he turned and strode off through the ward.

Dan ran his hand through his hair and headed to the cafeteria.

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[1] Multimodal Integration
[2] Theory Of Mind
[3] Exploration Intervention
[4] PsychoSocial

Chapter 10

Only three tables were occupied when Dan entered the cafeteria. Professor Krauss, Claire and Sonny were sitting at one of them. Dan smiled as the professor looked in his direction and waved him over.

‘Well, how is your first day in our department?’ Professor Krauss greeted him.

‘Good,’ Dan responded. ‘I am just going to get something to eat.’

‘Bring it back and join us,’ said Professor Krauss.

Dan went to the counter and the professor turned back to the two students and continued their conversation about psychiatric treatments. ‘It was not always good you know,’ he told them.

‘What do you mean?’ Sonny asked.

‘When I began my residency, at the turn of the century, psychiatry was in a poor state regarding effectiveness of Intervention, or as it was called then, effectiveness of treatment,’ said the professor. ‘All the brain perturbations to the dynamic core and global organization were once grouped under the single diagnosis of schizophrenia. Schizophrenia was basically an incurable disease at that time.’ He nodded as he recalled the past.

‘Professor Krauss, do you mind if I take notes?’ asked Claire.

‘Not at all,’ smiled the professor, his eyes twinkling as she pulled a notebook from her bag. ‘There were the so-called antipsychotic medications, but they changed brain organization from the segregated phase of disconnections and fragmented state-space to an over-integrated phase with constricted, limited and insufficient dynamic core.’

‘From one extreme to the other,’ commented Sonny.

‘Exactly,’ the professor stated. ‘The unfortunate patients would show the full consequences of reduced neuronal complexity and degradation of higher-level hierarchical formations. In those days, patients who suffered such consequences were considered to be suffering from negative symptoms, and psychopharmacology did not provide effective treatment for those symptoms.'

Dan returned to see all three looking solemn and shaking their heads, the action making Claire's glasses slide down her nose. She pushed them back up as Dan sat down. 'Professor Krauss is telling us about psychiatry in the old days,' she said.

'Ah,' said Dan and proceeded to eat his second lunch.

'We did not have the slightest idea about neuronal complexity and hierarchical organization at that time,' said Professor Krauss. 'Psychiatrists thought in terms of cause and effect, a way of thinking borrowed from general medicine, where one-step intervention produces a one-step linear and directly-related consequence. We did not use the nonlinear system approach in those days, so we lacked the basic methodology for dealing with mental disorders.'

'It all sounds too incredible,' said Sonny.

Professor Krauss continued. 'Back then, we did not understand the basic dynamics of mental disorders. How they appear suddenly as if out of the blue, for example. In physics, a critical point is where a system radically changes its behavior or structure, like from solid to liquid. In standard critical phenomena, there is a control parameter, which an experimenter can vary to obtain a radical change in behavior. In the case of melting, the control parameter is temperature.' The professor looked expectantly at Dan.

'A self-organized critical phenomenon,' said Dan, 'is when the dynamics of overworked systems reach a critical state regardless of any control parameter.'

'I'm not sure I understand,' Claire said hesitantly.

Professor Krauss explained. 'The best example of a self-organized critical system is a sand pile. Sand is slowly poured onto a surface, forming a pile. As the pile grows, avalanches carry sand from the top to the bottom of the pile. In model systems, the slope of the pile becomes independent of the rate at which sand is dropped. This is the self-organized critical slope.' He looked at Sonny and Claire but they did not question him, so he continued. 'Generally, we can define criticality as a point where system properties change suddenly, where a matrix goes from non-percolating—disconnected—to percolating—connected—or vice versa. This is often regarded as a phase change, so in critically interacting systems we expect step changes in properties and phase transitions in dynamics.'

'So,' said Dan, 'criticality may involve both levels as well as patterns of organization in systems.'

Sonny listened attentively while Claire continued taking notes.

'In phase transitions going from one level of organization to another,' said Professor Krauss, 'a system may gain or lose emergent properties in correlation with the transit to higher or lower levels of organization. For example, evolution is generally described as phases transiting from one level to a higher level of organization, therefore systems of higher level have more properties than the previous level system. Properties of a system can change abruptly according to the change of the organization pattern within the system.'

'Rachel and Todd are going to be very interested in this,' said Sonny. 'We take it in turns to locate research information and that's what they are doing now. This is something we would not have thought about.'

'No,' said Professor Krauss. 'It is not necessary for you to know how it was back then but it helps you to appreciate how far psychiatry has come in the last four decades.'

'Definitely,' said Sonny. Claire nodded enthusiastically, then pushed her glasses back up her nose.

Professor Krauss smiled. 'We psychiatrists,' he continued, 'did not have the slightest idea about complex system theories, let alone the complex system approach to psychiatry. The word complexity is defined as various parts connected together, composite, involved and intricate. Therefore, complexity is inseparable from the concept of systems.'

'You've lost me again,' said Claire.

Professor Krauss looked at Dan, who took his cue. 'Systems have elements and connections between the elements. Parts, units, and processes are all elements of systems they are interconnected to. They become interdependent, cooperate or compete for organization.'

'Organize,' said Sonny, 'means form a whole consisting of interdependent or coordinated parts, especially for harmonious or united action, and organization means the state of being organized.'

'Exactly,' smiled the professor. 'The concept of organization is therefore indistinguishable from the idea of systems.'

'Of course,' exclaimed Sonny, looking very pleased.

'The modes of interactions among the elements are crucial to the complexity of the system,' stated Professor Krauss. 'Elements can interact at random or in a more orderly manner. This leads us to another known definition of complexity, the KCS[1] definition, which places complexity somewhere between order and randomness. The KCS definition brings out the distinction between highly-ordered and highly-complex structures. Highly-complex systems are ordered but approach randomness, placing these systems balanced between order and randomness. Two aspects of complexity concern dissociation and connection.'

[1] Kolmogorov-Chaitin-Solomonoff

The professor turned to Dan, who was half-expecting to be tested again. 'Dissociation,' Dan explained, 'means variety and heterogeneity, where different parts of the complex system behave differently and independently. Connection means constraint, redundancy, where different parts are not independent and the knowledge of one part allows the determination of features of the other parts. Complexity can only exist if both aspects are present. Complexity is therefore situated between order and disorder, or you could say, on the edge of chaos.'

'That is a good description,' said Professor Krauss, nodding. 'Even though research psychiatrists[1] had long since appreciated these ideas of applying the complex system approach to psychiatry, psychiatrists in general began to appreciate this approach only after a doctor[2] presented the theory in his book[3].'

'This is really great,' said Claire. 'But I'm afraid we have a lecture to attend now. I hope you can tell us more another time, Professor.'

'I never disappoint an audience,' he replied, laughing.

Claire repositioned her glasses as she and Sonny left the cafeteria.

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[1] Such as Friston, Tononi, Copolov and Breakspear

[2] A Peled

[3] *Brain Dynamics and Mental Disorders*, 2004

Dan had finished all of his meal and was thinking how amazing it was that these obvious facts that Professor Krauss had just reviewed, were not mainstream psychiatry at the start of this millennium.

Professor Krauss must have read his mind, because he turned to Dan and said, ‘You know Dan, even before the beginning of this century there were some great authors that indeed recognized components of the system approach but they did not define it as such. Two centuries ago there was a great man[1] who was famous for defining brain structures responsible for sensory aphasia, disturbance of speech perception. He believed that the brain was organized as collections of reflex circuits, which developed to act in synchrony and that in schizophrenia their synchrony broke down[2]. That was an amazingly true intuition, what we now call segregation of the global organization or dynamic core.’

‘So long ago,’ commented Dan.

The professor’s tone changed to one of almost reverence as he said, ‘Later, a man[3] coined the term schizophrenia for what was previously called dementia praecox. Do you know why?’ Dan shook his head. ‘The term schizo meant splitting, he was convinced that in schizophrenia patients, mental functions were split and acted uncoordinated. He got this idea while observing the inappropriate behavior of his patients and assumed that the mental control over behavior in relation to mental control over thought-content was split, allowing for each process to proceed in an unrelated manner. In addition, he believed that the loosening of associations reflected splitting of conceptual activations. He then coined the famous four

[1] Wernicke
[2] 1881
[3] Bleuler 1913

'A's—affect, associations, ambivalence and autism—all reflecting some dissociation or split. For him, autism was social withdrawal, a form of social disconnection from others. His description of schizophrenia contrasted the previously used, purely descriptive term of dementia praecox, which meant early dementia. This described the dysfunction as being due to negative symptoms demonstrated by young patients.'

'It's fortunate for my first patient that he requires psychiatric care now and not back then,' said Dan.

Professor Krauss nodded and continued. 'Much has been contributed to the descriptive delineation of negative versus positive signs of schizophrenia[1], as well as to the idea that schizophrenia was a disturbance of organization of neuronal circuitry in the brain[2]. An elegant review[3] published in a leading scientific journal at that time, emphasized this direction of thinking. The author, an influential psychiatrist of world renown[4] promoted the systems approach in treating mental disorders. One year later, a paper[5] was published in a journal[6] and the author may have been the first to declare that schizophrenia is indeed a disconnection syndrome in the brain[7].'

Dan opened his mouth to comment on this information but was stopped by an announcement over the speaker system. 'Dr Moor, please pick up the house phone.' He looked around and the professor pointed in the direction of the exit.

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[1] Andreasen 1982, 1983, 1984, 1997, 1999
[2] Andreasen 1997, 1999
[3] *Linking mind and brain in the study of mental illnesses,* Andreasen 1997
[4] N Andreasen
[5] *The disconnection hypothesis*
[6] *Schizophrenia Research* 1988
[7] Friston 1998

Dan took the call and returned to the table. ‘My second patient has regained consciousness,’ he said. ‘I must go and complete my Investigation.’

‘Of course,’ said Professor Krauss. ‘I am due to give a lecture shortly.’ His eyes lit up at the thought.

Dan grinned and headed back to the ward.

Dan looked at his clipboard and read that Tim was a 32-year-old bank executive who had been involved in a car accident on his way to work.

'My name is Dr Moor,' Dan said as he entered the room and extended his hand to Tim. He dropped his hand when he realized Tim's hands were tied to the bed rails.

'Why is he restrained like this?' Dan asked the nurse.

'He became violent and tried to hit us when we came to take his blood pressure,' the nurse responded.

Dan turned back to Tim. 'What is your name?'

'Tim,' responded Tim in one blunt, short word.

'Where do you work Tim?' Dan asked.

'Tim,' he answered again.

'What is your profession?' Dan asked.

'Tim,' he repeated.

'He is severely perseverating,' Dan commented to himself, ticking the appropriate box on the PBP chart[1].

The interview proceeded and Dan became aware of severe blunting of cognitive functions. Tim was suffering from poverty of speech, severe repetitions and very concrete ideation. In addition, he totally lost control over his behavior, tending to cry frequently during the interview or become enraged as happened earlier with the nurses. Memory loss was pronounced but directed more toward ineffective working memory and short-term memory. On the PBP chart, Tim scored positions IP as well as positions 6, 7 and 8. This indicated reductions of dynamic core complexity, reduced state-space dynamics with perseverations, periodic attractors and reduced hierarchy of brain organization with blunt, reduced, concrete ideations.

[1] See Chart 1, appendix

‘Well,’ Dan said to the nurse, ‘Tim qualifies for what was once called frontal-lobe syndrome.’

Dan noticed that the nurse was looking at him blankly, so he elaborated. ‘For some time, it has been recognized that the frontal lobes of the cerebral cortex exhibit an organizing capacity for cognitive, perceptive, functions. A long time ago[1], there was a famous case of a man[2] which provided a startling demonstration of the effects of massive frontal lobe damage on personality functioning[3]. He was a railway worker involved in an accident where a metal rod went through his skull and destroyed his frontal cortex. Miraculously he lived but his personality and behavior changed radically. He went from being efficient, respected and dedicated to self-absorbed, rude and erratic. This demonstrated for the first time, the importance of this brain region. Later, it was established that executive functions are sensitive primarily to damage of the frontal lobe[4].’ He paused and looked at the nurse, who said nothing. He continued, ‘Impaired executive functions can also be seen with lesions in some areas[5], which likely reflects damage to the extensive connections between these other areas and the frontal lobes.’

‘Thank you Doctor,’ said the nurse, turning and leaving the room. Dan raised his eyebrows and let his thoughts continue on the subject.

It was noted[6] that the frontal lobes were the last of the cerebral structures to form in evolution and that they have become progressively more prominent in higher

[1] 1848
[2] Phineas Gage
[3] Damasio 1994
[4] including dorsolateral, orbital, and medial structures of the prefrontal cortex
[5] subcortical structures, including specific thalamic nuclei and areas of the limbic system, basal ganglia, and cerebellum
[6] Luria 1966

animals. This region, particularly the prefrontal cortex, was conceptualized as tertiary association cortex, theoretically responsible for coordination of information from various associated areas. It was stated that the relations of the frontal lobes to other brain regions enables us to understand the important role of the frontal lobes in the regulation of vigilance and in the control of the most complex forms of man's goal-linked activity[1]. In accordance with this theoretical framework, frontal structures demonstrate rich connections with many other brain regions, highlighting the importance of the frontal lobes in coordinating a variety of mental activities. The frontal lobe systems with their extensive connectivity with other brain regions are suitable neuronal brain constructs for the realization of the dynamic core and global workspace organizations at the highest levels of brain organization and complexity[2].

Dan brought himself back to the present and scheduled an MRE for Tim, to be applied at the Validation phase. Leaving the room, Dan realized that Tim was the second patient today he had scheduled for an MRE.

The MRE is widely used as it is the ultimate Validation tool of 2050 psychiatry. Walking back to the nurses' station, Dan recalled from his studies how the MRE gradually developed over the years by uniting three emerging scientific fields related to the brain. These were neuropsychological classical advancements, interactive computer technology, or more specifically virtual reality technology—VRT—and finally brain functional imaging and signal-analysis technology.

[1] Luria 1973, pp.187-188
[2] Mesulam 1998; Peled 2004

Chapter 13

Virtual reality—VR—is a set of computer technologies which, when combined, provide an interface to a computer-generated world. They provide such a convincing interface that the user believes he is actually in a three-dimensional computer-generated environment. This experience is also termed presence. A key feature of VR is interaction. The computer program responds to commands to enable the subject to act and react, participating in the computer-generated environment.

‘We meet again, Dr Moor,’ said a voice behind Dan, startling him.

Dan turned to see Helen right behind him. ‘You should wear a bell,’ he said with a mock frown.

Helen grinned. ‘Your patient will be returning from pathology, I’ll show you to her room.’ She guided Dan back down the corridor. ‘What were you deep in thought about?’ she asked.

‘Virtual reality,’ replied Dan.

‘Interesting,’ said Helen. ‘I know a little about that. The head mounted display—HMD—is a helmet or facemask that holds a visual stereoscopic and auditory display. The HMD also has a position tracker to enable the effect of eye tracking and head rotation in the exploration of the virtual environment. The audio component of the HMD provides the relevant sounds generated by the virtual environment.’ She looked at Dan, who smiled and nodded for her to continue. ‘To enhance the auditory virtual sensation a head relevant transfer function—HRTF—program provides for three-dimensional sound recognition. The data glove—DG—is a special glove designed to manipulate objects in the virtual environment. This glove is equipped with sensors for finger bends and magnetic trackers for overall position, which allows the wearer to project real hand movements into the artificial environment. Haptic rendering—HR—is the generation of touch and force-feedback information.'

Dan nodded. 'Correct,' he said. 'The use of VR in psychiatry at the beginning of the century was directed especially towards the treatment of anxiety disorders. These included phobias, such as fear of heights, flights and insects[1], where the virtual experience was modeled for desensitization therapy. In anorexia nervosa, body image was projected into the virtual world for feedback of body dimensions[2].'

'I recall hearing about the work on bedside wellness system—BWS,' interjected Helen. 'The creation of a pleasing environment for bedridden oncology patients improved their reaction to treatment and their coping capabilities[3].'

'At the start of the century,' continued Dan as they rounded a corner, 'VR technology had already been preliminarily applied to cognitive assessments and rehabilitation in neurological disease such as traumatic brain injuries[4]. Initial insights obtained from cognitive assessment with VR technology were beginning[5].'

'Traditional neuropsychological testing methods,' stated Helen, 'were limited to measurements of specific, theoretically predetermined functions such as short-term memory or spatial orientation.'

'Yes,' agreed Dan. 'Given the need to administer these tests in controlled environments, they were often highly contrived and lacked ecological validity, or any direct translation to everyday functioning[6]. VR enabled subjects to be immersed in complex environments that

[1] Bullinger et al. 1998; Rothbasum and Hodges 1999
[2] Riva et al. 2003
[3] Oyama et al. 2000
[4] Christiansen et al. 1998
[5] Rizzo 1999
[6] Rizzo 1999

simulated real world events and challenged mental functions more ecologically. While existing neuropsychological tests obviously measured some brain mediated behavior related to the ability to perform in an everyday functional environment, VR allowed for cognition to be tested in situations that are ecologically valid. Quantification of results in traditional testing was restricted to predetermined cognitive dimensions, whereas with VR, many more aspects of the subjects' responses were measured. This included things such as latency, solution strategy and visual field preferences. VR immersed subjects in situations where complex responses were required and measured all responses in this environment[1].'

'That's VR, what about VRT?' asked Helen, leading Dan into a room.

Dan sat on the end of the empty bed. 'Virtual reality technology —VRT,' he answered, 'was actually the next level of achievement in respect to traditional cognitive assessments. In the traditional assessments of frontal lobe functions—what we understand today as the higher-level transmodal integrative functions—a battery of tests was applied, which included the assessment of attention memory learning and executive functions.'

'What tests were they?' queried Helen.

'For the MRE, the tasks for assessment of these same functions were Digit-Symbol or Symbol-Digit, Ruff 2 & 7 Selective Attention Test, Paced Auditory Serial Addition Test, Continuous Performance Test, Stroop Color Word Naming Test and Trail Making A and B test for assessment of concentration. As well as Rey Auditory Verbal Learning Test, Selective Reminding Test and the California Verbal Learning Test for the assessment of memory and learning. And finally, Controlled Oral Word Association Test, Ruff Figural Fluency Test, Wisconsin

[1] Rizzo 1999

Card Sorting Test, Category Test and Stroop Color Word Naming Test, for the assessment of executive functions. All these tests were altered, adapted and merged to make part of a virtual environment that challenges all the higher-level brain functions in parallel, namely, mental flexibility, ability to maintain cognitive sets, divided attention and goal directed decision-making[1].'

'What a long, involved process it must have been,' commented Helen.

Dan nodded. 'There were those[2] who first published initial results involving such challenges in schizophrenia patients. A V-Store program was used[3] that allowed traumatic brain injury—TBI—patients to explore a virtual environment where they solve series of tasks with increasing complexity.'

'But when did the MRE come into it?' asked Helen.

'In the second decade of this century,' said Dan, 'enough data had been accumulated about integrating these tasks to assess higher-level brain functions that the coupling of these assessments with imaging advancements created a powerful brain measurement tool that led to the multimodal reconstructive encephalography—the MRE as it is known today. The imaging component, with its powerful signal analysis capabilities, formed the MRE as the major Validation tool for psychiatric mental dysfunctions.'

They both turned towards the door as a nurse pushed a wheelchair into the room.

'I'll leave you to it,' said Helen, smiling at the nurse and patient.

Dan stood up as Helen disappeared through the door.

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[1] McDonald et al. 2002
[2] Such as Sorkin, Peled, Weinshel (in preparation), Ku et al. 2003
[3] Priore and colleagues 2003

Chapter 14

Dan read the patient information sheet while the nurse settled the young woman in the bed. Pamela was 25 years old and was hospitalized following a suicide attempt using an overdose of sleeping pills. Dan looked over at her pale face, framed by dark cropped hair that matched the circles under her eyes.

‘All set now,’ said the nurse cheerfully. She gave Dan a quick smile and left the room, pushing the wheelchair in front of her.

Pamela was sitting in the bed, still connected to the gastric lavage sonda. ‘Who are you?’ she asked. The protruding apparatus, used to administer the solution for washing out her stomach, made her speech sound nasal.

‘Hello Pamela, my name is Dr Moor,’ Dan introduced himself and started his Investigation interview.

‘Why did you attempt suicide?’ he asked.

‘I was feeling lonely and desperate with nothing to live for anymore,’ said Pamela.

‘When did you begin to feel that way?’ Dan asked.

‘I often feel like this and I get depressed now and then,’ answered Pamela.

‘I see,’ Dan said. ‘When did you start feeling so desperate this time?’

‘Well, it started last weekend,’ said Pamela.

‘Did anything in particular happen lately, or during the weekend?’ asked Dan.

‘My boyfriend decided to go to his parents’ for the weekend instead of spending the time with me like he usually did,’ said Pamela. She had taken this badly, feeling unwanted and rejected, spending the entire weekend in bed, feeling depressed. ‘He didn’t want me because I’m nobody, a failure. It’s my fault he rejected me.’ Pamela closed her eyes briefly.

‘Is that when you decided to try to kill yourself?’ Dan asked quietly.

‘I felt so hopeless and worthless and thought that I would be better off dead.’ She had begun thinking about taking all the pills she had at home. ‘I thought I would probably go to sleep and just die without waking up.’ The next morning, Pamela had woken feeling deeply depressed, so she had gone to the drawer where she kept the pills and swallowed them all. ‘After a few minutes I started to feel nauseous and had painful abdominal cramps. I called a friend from work, who called an ambulance. I was brought straight to the emergency room.’

As the interview went on, Pamela’s background was gradually revealed. Dan noticed that Pamela’s suicidal feelings and periods of depression would build up following social interpersonal events where she felt that she did not get the attention and affection she deserved. Typically, these were also situations where she was criticized, and even mild criticism would trigger feelings of worthlessness to the extent of total despair and suicidal thinking.

This caused Dan to think towards the diagnosis of system configuration and state-space maturation, once called personality disorder. To get the relevant information about the development of Pamela’s state-space configurations and her system of reference of internal representations, Dan extended the interview to gather detailed, meticulous information about Pamela’s interpersonal relationships from birth to adulthood, as well as her coping behaviors in generally critical phases of life events and also within interpersonal social events.

Dan looked up from his notes and saw that Pamela had fallen asleep. He decided to let her rest for a while and went to get a cup of coffee from the machine in the visitor’s waiting room.

On the way, Dan recalled the revolutionary thinking in the field of personality disorders that started with the uniting of psychological formulations from the previous century with the neuroscience findings from the start of this century. First attempts to combine the knowledge were made by formulations of a connecting language between these distinct and apparently distant disciplines[1].

Dan entered the waiting room and went straight to the machine, oblivious to the other occupants of the room. He was contemplating mapping out the landscape of internal representations achieved by Pamela's brain.

Dan remembered that this approach was first formulated as such by the writings of a doctor[2]. Using the state-space formulation, a memory embedded in the model[3] forms an attractor—basin—on the state-space manifold of the model[4]. The attractor represents the dynamic tendency of the system to activate the memory states. Multiple attractor formations in the state-space manifold of a system provide for internal information embedded in that system, so that the manifold topography of a dynamic structure is shaped to reflect the internal representations achieved by that system.

Dan picked up his cup and went to stand at the window, looking out at the well-kept grounds below. He sipped his drink while his thoughts continued.

Since the brain, as a complex non-linear system, operates balanced between orderliness and randomness, the internal representations are subject to continuously changing influences. A more complete description of the functional connectivity of the brain is related to the

[1] Peled 1999, 2004
[2] Peled 2004
[3] Hopfield
[4] Hopfield 1982

statistical structure of information sampled from the environment. This information activates specific neural populations and, as a result, synaptic connections between them are strengthened or weakened. In the course of development and experience, the fit or match between the functional connectivity of the brain and the statistical structure of input from the environment, tends to increase progressively through processes of variation and selection mediated at the level of the synapses[1].

Dan reflected again on the concept of matching complexity and the introduction of this statistical measure. The internal representations, embedded as statistically input-matching patterns, are continuously altered by the configuration of external influences. Once altered, the consecutive inputs are interpreted by the recently altered internal representations. As early as the previous century the terms assimilation and accommodation described this idea[2]. Assimilation is when new patterns of experience are incorporated and accommodation is the use of the assimilated experiences in life situations. The interactive assimilation-accommodation feedback drives human mental development.

[1] Edelman 1987
[2] Piaget 1962

Chapter 16

Dan finished his coffee and glanced around the room. He was surprised to see Todd and Sonny looking at him.

‘Hello,’ said Dan. ‘I didn’t see you two there.’

‘You looked very deep in thought,’ said Todd ‘So we didn’t want to disturb you.’

‘I was thinking along the lines of something we were discussing this morning,’ said Dan.

‘We have ten minutes before we meet the doctor we are to accompany on his rounds,’ said Sonny. ‘So, if you would like to share your thoughts we would be interested to hear them.’

‘I remember very early psychological notions,’ Dan began, ‘relevant to the idea of internal representations as configuration landscapes or maps in the brain.’

‘Ah yes,’ laughed Todd, ‘Rachel’s scenery.’

Dan grinned and continued. ‘A famous psychologist[1] suggested that the best vantage point for understanding behavior is from an internal frame of reference of the individual himself. He called this frame of reference the experiential field, and it encompasses the private world of the individual. Neuroscience demonstrates that the brain uses internal maps to represent information. One example is the homunculus of sensory and motor representations spread over the cortex[2].’

‘The homunculus,’ said Sonny. ‘Isn’t that a representation of the body with areas of high sensitivity occupying more space than those of lesser sensitivity, giving a distorted image?’

Dan nodded. ‘Just as the homunculus is probably formed from the strengthening of synaptic pathways, the experiential field probably results from experience-

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[1] Rogers 1965
[2] Roland 1993

dependent plasticity in the brain[1]. In terms of space-state formulation, the experiential field can be described as a configuration of attractor systems in the brain.'

'I hope you don't mind, Dr Moor,' said Sonny, as he began jotting notes. 'You are a lot easier to follow than most of our research material,' he told Dan.

Dan shook his head. 'No, go ahead,' he said. 'Organismic evaluation is the mechanism by which a map—the internal configuration—of the experiential field assesses the psychological events of everyday life[2]. Using the description of state-space configuration, organismic evaluation can be thought of as convergence into, or activation of, relevant experience-dependent attractor configurations of the internal map. If the incoming experience is identical to the previous internal representation of that experience, no change will occur and the map of internal representation will activate familiar past experiences.'

'And if the experience is not the same?' questioned Todd.

'If the new experience is slightly different from the past experience,' answered Dan, 'this will be enough to reshape the topological map and add attractor configuration to the internal map of references.'

'So what you are saying,' said Todd, 'is that activation of the internal map organizes the incoming stimuli into a meaningful perception.'

'Correct,' confirmed Dan. 'The newly perceived experience is meaningful when it relates to the previous experience already embedded in this map. This is a circular process where the map of internal representation is both influencing and being influenced by the incoming stimuli at the same time.'

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[1] Kandel 1979; Friston 1996
[2] Rogers 1965

‘In other words,’ said Sonny, ‘The brain keeps a map of internal representations that is continuously updated through interactions with the environment.’

‘Right,’ said Dan. ‘Later on, this type of interaction between internal representations and perception of environmental stimuli was referred to as context-sensitive processes[1]. Due to this interaction, internal representations can be viewed as approximated models of reality.’ Both students nodded slowly.

Dan continued, ‘It is reasonable to assume that a good match between internal representations, of the psychosocial world, and external psychosocial situations will enable efficient adaptive interpersonal relationships. On the other hand, a mismatch between the psychosocial events of the real world and their internal representation may deform or distort the perception and the behavioral responses of the individual. In addition, reduced matching complexity will further reduce adaptability causing rigidity, reducing the repertoire of reactions available to the individual.’

‘And that’s when problems arise,’ stated Todd.

Dan nodded. ‘Incoming information is evaluated by the internal representations that are formed by experience, so it is only natural that many of the perceptions we have are related to past experience. When sets of input from a new interpersonal event interact with the neural system, they activate a set of attractors representing past experiences similar to the new interpersonal situation. If there is a substantial mismatch then transference—a distortion of the actual situation—may occur. Matching complexity may be the future mathematical tool that will predict to what extent transference is likely to determine one’s behavior.’

[1] Friston 1998

Sonny frowned slightly. ‘Where does denial come into it?’ he asked.

‘Sometimes,’ explained Dan, ‘a current experience is so far removed from any context of past experience that it becomes entirely unperceived by the individual. This is defined by psychodynamic terminology as denial. An individual with narcissistic personality traits may not recognize signs suggesting that he is not desired. This is because in his map of internal representations there is no context—attractor system—that represents rejection. Since the representation of rejection will not be activated at all, it will not manifest in the global organization of state-space and will remain entirely out of any conscious awareness. And that is denial.’

Looking at his watch, Dan said, ‘I must go and see if my patient is awake. Please excuse me.’

‘Of course,’ said Todd as Sonny nodded.

Chapter 17

Dan walked briskly back to Pamela's room and was pleased to find her awake. There was a woman with her, who introduced herself as Margaret, Pamela's mother. Dan took advantage of this as the interview would now meticulously cover the development of Pamela's life.

'Margaret,' said Dan 'Tell me about Pamela as a baby.'

'She was a good baby,' stated Margaret. 'She cried little and would stop as soon as I picked her up. I took very good care of her, providing everything a baby should have.' She smiled at Pamela. 'My daughter and her happiness have always been the most important things in my life,' she declared.

'Thank you, Margaret,' said Dan, 'that is very helpful. Would you mind adjourning to the visitor's room while I complete my interview with Pamela? The nurse will advise you when you may return here.'

'All right,' said Margaret. She kissed Pamela's cheek and patted her hand. 'I'll be back soon,' she told her.

As Margaret had immediately satisfied Pamela's every need as a baby, Pamela never knew frustration from delayed satisfaction of her needs. As the interview progressed, it was apparent that Pamela's early life experiences were shaped by her primary care-giver, her mother, who was over-protective. This over-protectiveness and immediate satisfaction evolved throughout Pamela's life, with Margaret intervening in every conflict or hardship that could have annoyed Pamela. She intervened on Pamela's behalf at kindergarten so that Pamela was privileged and never suffered aggravation caused by other children. Later at school, if the teacher was too critical of Pamela, her mother complained to the headmaster and the teacher was told not to be too demanding or critical of Pamela.

His interview finished, Dan left Pamela and went back to the staff lounge where he hoped to find Professor Krauss. He asked the nurse at the station to let Margaret know she could return to Pamela's room. As he walked along the corridor he thought how hard it was going be to treat Pamela.

Dan arrived at the staff lounge and was disappointed to find the professor was not there. He made himself a cup of coffee, which he took into his small office, and sat down to read through his notes.

Thinking about the idea of experience-dependent plasticity, which shapes internal representations in the brain, it was no wonder that Pamela's brain never developed an inner representation of exasperation or frustration. The mismatch between external affairs and internal representations emerged from her mother's need to adopt external affairs to Pamela's internal representational structure of internal configurations. Since Margaret exerted a lifelong matching of external events to internal representations, this matching in itself was the cause of delayed maturation of the internal representations.

This was obvious in the light of matching complexity having to do with the increase of statistical structure and complexity in the nervous system. The lack of mismatch caused a deficiency in the process of matching complexity, which impaired the development of internal complexity[1]. Not only did Pamela lack specific experience-dependent representations to cope with frustrating situations, she also suffered from delayed and restrained development of complexity measures within her brain organizations.

Dan concluded that Pamela's major problem involved an immature state-space configuration[2] and the

[1] Tononi and co-workers

[2] See chart 1, Appendix

state-space organization fitted somewhere between the unstable and primary levels, which were once called borderline and narcissistic personality organizations. Pamela tended to perceive psychosocial events in an all-or-none mode and had difficulty stabilizing her optimization dynamics—her feelings and behavior—but was still functioning at a higher level of emotional-mental capabilities than the lower level of unstable state-space configuration. Pamela's non-adaptive, reduced complexity transmodal brain systems combined with her inability to adapt to the temporary loss of her boyfriend that weekend. This, together with her lack of internal representations for delayed satisfaction, caused a deoptimization shift in the global dynamics of her brain neural network systems. Depression developed as an emergent property from the deoptimization dynamics. Once deoptimized, everything Pamela processed in terms of thinking and feeling had a pessimistic tone. She saw no future for herself, and in this context, suicide was a reasonable thing to do.

Dan reflected that such protective relationships had deprived Pamela of any frustration experiences regarding delayed satisfaction or interpersonal disapproval. Dan marked an additional position number 2 on the matching complexity perturbation channel for deoptimization on the PBP chart[1]. The complete diagnostic code for Pamela was Ps and Cs, denoting past stressors for her mother-daughter relationship and current stressor for the leave of her boyfriend, [P] for primary state-space configuration and 2 for deoptimization dynamics.

[1] See chart 1, Appendix

Chapter 18

Dan looked up expectantly at the sound of approaching footsteps and was pleased to see Professor Krauss through the doorway. ‘Professor,’ said Dan. ‘I was hoping to meet up with you here,’ he said, getting up and taking his cup into the lounge.

‘And now you have,’ said the professor with amusement. He went to make himself a drink and they sat down. ‘So what seems to be the problem?’ he asked.

Dan told Professor Krauss about Pamela and her over-protective mother.

‘The ideas of early object relations psychologists and state space neuroscience formulations of brain systems fit so well,’ said Professor Krauss. ‘Object relations are dynamic internal representations of reference and it is according to them that the individual perceives his or her psychosocial environment. State-space formulations show how a dynamic neural network system can form configurations that, when activated, can actually come to pass the idea of object relations and dynamic internal representations.’

‘It is astounding that this fit between the different formulations of the diverse fields was not recognized earlier,’ said Dan. ‘It was only at the start of the century[1] that it became apparent.’

‘Other, even earlier, psychological formulations fitted well with late neuroscience insights,’ stated the professor.

‘So,’ said Dan as realization dawned, ‘psychologists were the first to achieve certain accuracy in describing whole brain functions.’

[1] *Brain Dynamics and Mental Disorders, Project for a scientific Psychiatry*, Peled 2004

‘True,’ nodded the professor. ‘The first concepts introduced in a topographic model[1] related to the levels of consciousness. We now have the tools to define this description of conscious, unconscious and subconscious as levels of integration that partial processes achieve to form the global organizations of the dynamic core. Conscious awareness is the property of global integrations. Partial processes that do not make part of the global organizations present unconscious information. Those processes that are about to make part of, or drop out of, the global formations characterize the subconscious.’

Dan sipped his drink, casting his mind back to what he had read about Freud. ‘In the structural model,’ he said, ‘psychic compartments such as the ego and id were added[2]. The ego develops from where initially all was id in the infant.’

‘The id is described as a disorganized system where concepts are disconnected or dissociated in every strange possible way,’ added Professor Krauss. ‘This form of inconsistency was named the primary thought process[3]. From this point of view, primary thinking can be described as a feature of a system without internal consistency. That is, one where multiple constraints are abolished. This enables conflicting ideas and nonsense concept-formations to coexist and pre-dominate consciousness. Biological evidence shows that in infants, synaptic connectivity is premature[4].’

‘In which case,’ said Dan, ‘the neural substrate cannot support the needed multiple-constraints organization that forms the basis of ordered mental activity.’

‘Ego,’ said a voice from the doorway.

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[1] Freud 1953
[2] Freud 1953
[3] Freud 1953
[4] Roland 1993

Dan and Professor Krauss turned to see Dr O'Connor standing just inside the door. 'The development of the ego involves the formation of secondary thought process[1], a process described by Freud as normal thinking. Secondary thinking emerges from multiple-constraint-satisfaction organization of the neural system, and synaptic connectivity matures from infancy to adulthood.'

Professor Krauss nodded as Dr O'Connor continued, 'By introducing the concept of superego, internal representations of social and interpersonal norms were suggested. It gave the ego—its superego portion—not only the scope of organizing the disordered id processes but also the entire responsibility of representing and adapting to psychosocial reality.' He looked at Dan and announced, 'I have been called away Dr Moor. We will discuss your patients when I return.'

Dr O'Connor nodded once to the professor and left. Dan raised his eyebrows as he looked at the place where Dr O'Connor had been standing.

[1] Freud 1953

'Dynamic model,' said Professor Krauss, bringing Dan's attention back to their discussion. 'Introduction of the dynamic model[1] added interplay of drives among the psychic compartments of the model. Defense mechanisms are probably the dynamic factors most accounted for in this model. It was said[2] that the ego makes use of an unconscious domain of mental activity, the id, into which undesirable drives and ideas are repressed.'

'Repression,' said Dan. 'That has been described as the mental mechanism that guards the conscious awareness from the intrusion of inadequate and intolerable ideas or drives. It was indicated[3] that the intruding ideas and drives from the unconscious actually threaten ego integrity.'

The professor put his hand to his chin and leaned back. 'Repression can be re-conceptualized as the dynamics of participating, as well as non-participating, processes in the global formations that support conscious phenomena. Partial processes that do not gain access to the global process remain unconscious, repressed. The multiple-constraints that characterize global organizations mean that certain partial processes may encounter difficulty in accessing the global formations. This is especially true if the partial processes carry information—or arrangement pattern—that is entirely different from, or contradictory to, global organization. Based on these assumptions, it is possible to conceive what type of information will be denied access to the global organization.'

'The contradictory and unfitting messages,' said Dan.

'In neuronal terms, it will be the partial arrangement pattern that does not satisfy the constraints of global

[1] Freud 1953
[2] Freud
[3] Freud

arrangements,' said the professor. 'In fact, the repressed contents were described[1] as conflicting topics or unbearable ideas—with unbearable meaning the partial process that does not fit the information pattern presented by the pattern of the global integration.'

'If the idea is unbearable,' said Dan, 'the partial process cannot be incorporated in the general message without damaging its internal consistency and integrity, so it is bound to be excluded.'

'An example,' said Professor Krauss, looking directly at Dan, 'is that of the mother of a newborn baby. The idea of killing her baby is extremely contradictory to the regular loving and caring state of mind typical to a new mother. If inadequate partial processes somehow gain access to the global organization they are inclined to destabilize or even disrupt it. If many conflicting and disrupting processes gain access to the global formation, the whole global message may be destroyed and the neural system representing it is bound to destabilize. Indeed, the types of thoughts which involve killing one's newborn baby often emerge in mentally disturbed patients.'

Dan was almost talking to himself when he responded. 'Then it is conceivable that certain partial processes do, in fact, threaten the integrity of global formations and the actual stability of the dynamic core.' He leaned forward excitedly. 'And this conforms to the notion of ego integrity that is being threatened by repressed mental processes of conflicting ideas or drives.'

The professor too, leaned forward, his eyes bright. 'Occasionally, inadequate partial processes may gain access to the global organizations and are transformed in order to accommodate the global pattern. For example, an immoral idea is contradictory to the dominating content of a moralistic conscious awareness. Transforming the wish to

[1] Freud

behave in an immoral way into a moralistic idea may accommodate the dominating global organization of a puritanical message.'

Dan held up his finger. 'That type of transformation is known as reaction-formation in psychoanalytic literature.'

'It is,' the professor confirmed.

'There is another transformation of unbearable ideas,' said Dan, 'known as isolation.'

Professor Krauss inclined his head then looked attentively at Dan, who continued. 'In isolation, the idea is not excluded from awareness but certain relevant parts of it are neutralized. These are the parts that are incompatible with the rest of the conscious message. The partial process is included in the conscious awareness but is isolated so that it is kept apart from certain contents of the conscious awareness. If isolation is not enough to satisfy the message of the global integration then dissociation might occur and certain contents of awareness would be ignored or experienced as independent and unrelated.'

The professor's face became serious. 'The transformations are needed in order to protect the global formation from being disrupted by contradicting partial processes. Therefore, it is conceivable that these transformations justify the term defense mechanism. They protect the global formations and prevent destabilization of the dynamic core. From the biological point of reference, this may translate into destabilization of the interrelations between groups of neurons, which presumably has direct neuro-pathological outcomes on transmitter-receptor activity.'

Chapter 20

Professor Krauss leaned back. 'Those[1] who developed what was later termed object relation psychology, concentrated on the study of the dynamics of internal representations and their relevance to personality and personality disorders. Personality traits are enduring patterns of perceiving, relating to, and thinking about the environment and oneself. They are exhibited in a wide range of social and personal contexts[2]. Specific configurations of internal representations have first-hand impact on personality traits. For example, internal representations regarding hygiene, punctuality and precision, are more pronounced for some individuals, while for other individuals different representations are prominent , such as vanity and pride.'

'The first example you mentioned,' said Dan, 'is typical of people who give special importance to order and strive to achieve perfection. They are often referred to as having obsessive personality traits. The second example is more typical of those who regard themselves as special and important, often referred to as having narcissistic personality traits. Those who attribute importance to hygiene optimize these internal representations of context and will perceive stimulus carrying information of dirt and filth differently than individuals who do not have this type of attribute.'

Professor Krauss nodded in agreement. 'That is correct,' he said. 'Once decoded, the map of internal representation can both explain and predict the reaction of the individual to certain stimuli. In the case of personality disorders, the optimization of particular internal representations of context may be enhanced to the extent where certain stimuli may be perceived with incredible

[1] Such as Winnicot, Klein and Mahler
[2] Sadock 1989

distortion. For example, someone with an obsessive personality disorder may perceive even a little dust on the table as extreme filth. An individual with a narcissistic personality disorder may interpret even slight disapproval as an extreme insult.'

Dan held up his index finger. 'The formation of specific configuration maps in different individuals depends on the background of the individual,' he said.

'Yes,' responded the professor. 'Individuals reared in families that give emphasis to being sanitary will probably encode this emphasis through experience-dependent-plasticity. Individuals reared in environments in which they were considered of prime importance and were the center of attention will probably incorporate these attitudes by optimizing the need to receive affection and attention—narcissistic traits. The experience-dependent processes that form internal representations may involve deviations from the normal itinerary of internal representations needed for regular psychosocial function. The internal representations formed by these deviations may be greatly removed from psychosocial reality. A large mismatch between the internal representations and the environmental reality is likely to provoke distortions that lead to disturbances in perceiving and reacting to the environment.'

'And there you have personality disorders,' said Dan.

Professor Krauss nodded slowly. 'A large mismatch is likely to create the same difficulties that conflicting partial processes may encounter when trying to gain access to global organizations of conscious awareness. This mismatch may distort the incoming information. A good example of this distortion is seen in the phenomenon of transference.'

'Ah, yes,' said Dan. 'Transference is a distortion within interpersonal relations, it occurs when people are perceived not as they are, but rather as somebody who resembles them from the past[1]. In which case, the perception of the person is distorted to fit the internal representation of a similar person encountered in the past.'

'Now,' said the professor 'I am to attend another meeting.' He smiled as he stood. 'Finish your notes and go home Dan.'

'I will,' replied Dan. 'It has been a great relief to discuss things with you, Professor Krauss. Thank you.'

'My pleasure,' said the professor and waved as he left the room.

[1] Michael 1986

Chapter 21

Dan went back into his office and ruffled his hair as his thoughts returned to Pamela. He summed up that personality assessment equals the assessment of internal representations. The internal map of organismic evaluation can be reconstructed by unfolding the subjective experience of the patient and the patient's perception of the world, especially of interpersonal experiences. Once reconstructed, this internal map of representations is a powerful predictor of the reactions and interactions that the patient will demonstrate. It could easily be predicted what the patient with internal optimizations of orderliness and hygiene will experience when confronted with filth and dirt conditions.

As well as the features and content of internal representations, the levels of their development also warrant assessment. Rudimentary maps allow for partial and opposing representations to split experiences. Partial development of internal representations induces all-or-none experiences—black and white attitudes. This impedes complex experiences—varieties of grey attitudes—and allows denials. Summing up again, Dan thought that the assessment of internal representations follows two dimensions in parallel—the development levels and the content features.

He noted that Pamela suffered from both immature, complexity-reduced, brain organizational systems as well as biased internal configurations. Having reduced complexity levels, she interpreted much of her relationships in an all-or-none mode. If her boyfriend did not come that weekend it meant total rejection. Having no internal representations of frustrations due to criticism or denunciation, Pamela was not equipped to adapt to loss and rejection. This lack of adaptation curtailed her optimization dynamics, creating the depression as an emergent property of deoptimization.

Dan looked up as he became aware of someone in the staff lounge. He heard a person getting a drink of water from the dispenser.

‘That’s it for me for the day,’ said a voice he recognized as Helen’s.

‘Me too,’ said Dan. ‘I have just finished my notes.’

‘Good,’ replied Helen with a grin as she appeared in the doorway. ‘You can explain optimization to me on the way to the car park.’

Dan raised his eyebrows and gathered his belongings into his briefcase.

Chapter 22

Dan started speaking as the two of them left the staff lounge. 'To explain optimization, it was acknowledged[1] that in complex systems the dynamics of constraint satisfaction among the units in the brain are continually changing. They can proceed in either of two directions, one is optimization, when more constraints become satisfied over time, and two is deoptimization, when fewer constraints are satisfied over time. It was proposed[2] that optimization correlates with the emergent property of elevated mood and deoptimization correlates with depressed mood.'

'So, one would speculate that mood is an emergent property related to the level of optimization dynamics within the dynamic core?' suggested Helen.

'Right,' acknowledged Dan. 'Optimization dynamics takes into account the configurational space of internal representations because the various configurations and arrangements of state-space are optimized. Optimization dynamics also involves sets of incoming stimuli from environmental and psychosocial events. This is because their interpretation involves activations and optimizations of the configuration map with its various internal representations.'

'What about deoptimization?' asked Helen.

'Normally, optimizations and deoptimizations occur mixed together,' explained Dan. 'The information processing in the brain optimizes certain internal configurations and deoptimizes others in a parallel manner. In this way, the overall dynamics is stabilized between numerous optimizations and deoptimizations.'

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[1] Peled 2004
[2] Peled 2004

‘Making the emergent property of mood balanced as well,’ finished Helen.

‘Right again,’ laughed Dan. ‘However, if many configurations are deoptimized and a shift of balance toward deoptimization takes over the system, this will result in a depressed mood. Homeostatic mechanisms will probably act to balance this dynamic shift by triggering optimization dynamics to counteract the deoptimizations in the system. If the system is taken over by swings between optimizations and deoptimizations, mood will also alternate between mania and depression.’

‘Ah,’ said Helen ‘The well-known manic-depressive disorder.’

Dan nodded. ‘Yes.’

They walked in silence until Helen said, ‘I follow what you said but I’m not sure I completely understand how optimization of internal representations can be relevant to mood changes.’

‘Well,’ said Dan and thought for a moment. ‘It was assumed[1] that based on past experience—experience-dependent plasticity—the brain has acquired a set of internal configurations—the attractor formation in the space manifold—to represent, let’s say, succeeding in an exam in which there is a socially favored achievement. Now, assuming that the person with such internal representation has taken an important exam and has just received the news, which is the information stimulus, that he has passed the exam, the interaction of such information with the map of internal configuration will shift part of the system dynamics towards an optimization mode of activity. Such a shift would emerge as a feeling of satisfaction, an elevated mood. In the unfortunate case of failing the exam, the same internal configurations would be deoptimized, resulting in a depressed feeling, disappointment.’

[1] Peled 2004

Helen looked across at Dan. ‘I see,’ she said.

‘That example is oversimplified,’ Dan continued as they approached the main entrance. ‘The complexity of internal representations, as well as the dominant patterns of dynamics in the system, also needs to be considered. The internal representation of succeeding in the exam could be interconnected with many other internal representations that may extremely amplify the effect of optimization. For example, if the internal representative configuration of succeeding in the exam is linked to the internal representative configuration of love from a parent, then feeling loved by the parent can be associated with the optimization dynamics of success in the exam, amplifying substantially the mood effect of this achievement.’

Dan could see Rachel and Claire standing outside the building. When he and Helen walked out, the two students took a step towards him.

‘If you could spare us a minute please Dr Moor,’ said Claire, ‘we would like to speak with you.’

Dan turned to Helen. ‘I’ll leave you to it,’ she said with a grin.

He watched her disappear around the corner of the building then turned to the girls. ‘What can I do for you?’ he asked.

Chapter 23

'Shall we sit over there?' suggested Rachel, pointing to one of the many bench seats placed around the grounds.

'We know that in global formations,' said Rachel as they walked to the seat, 'there are internal consistencies and these form multiple constraints between the partial processes. We discussed that at lunch.'

They sat down and Claire pushed her glasses up her nose as she said, 'We—all four of us—are a little confused about satisfaction and frustration of constraints.'

Dan waited for them to get their notebooks ready before he began explaining. 'Whenever constraint satisfaction in the brain tends to be disturbed, frustration of the connection between the elements in the system occurs,' he said. 'Frustration is the term used[1] to indicate that connections are only slightly unsatisfied. Frustration of constraints means that the elements of the system are not acting in complete agreement with the multiple connections among them. The elements in such a system will change their states, their values, in an attempt to reach full satisfaction of the constraints. They will continue to change as long as frustration of constraints characterizes the system.'

The girls looked up from their note taking. Clare gave a nod for Dan to continue, which made her glasses slide down her nose again.

Dan suppressed a smile and went on. 'Since the brain is a dynamic system[2], once connections are satisfied, the system has already changed and a new set of constraints needs satisfaction. So, a certain degree of ongoing frustration is typical to the system of the dynamic core. If the frustration of the constraints increases, the dynamic

[1] Peled 2004
[2] Globus 1992

process of constraint-satisfaction increases. This causes the elements to change their states more abruptly. If the frustration of constraint increases to where it surpasses the dynamic ability of the elements to change their states, a danger of breakdown threatens the connections.'

Rachel held up her hand for Dan to pause while she jotted furiously. Still taking notes, she pointed at Dan for him to continue.

Amused, he said, 'Since the dynamic core has a massive connectivity structure, multiple constraint frustrations can spread over many connections in the cluster system. To some extent, these can be absorbed by the interconnected structure of the system. This process of absorbing the frustrations of the constraints maintains the stability of the global integration within the dynamic core.'

'What if all the frustrations aren't absorbed?' asked Rachel.

'Good question,' said Dan. 'It was suggested[1] that whenever the degree of frustrations applied to the multiple connectivity of the system exceeds the level where it can be absorbed, the system is destabilized and the risk of rupture to the connections becomes prominent. At this level of disturbance, elements in the system change rapidly in a desperate attempt to satisfy their connections. It was suggested[2] that anxiety is the emergent property from this type of instability in the neural systems, especially in those neural systems that are involved in global formations, such as transmodal processing systems of the dynamic core.'

'Ah, you found him,' said a male voice. The three turned to see Todd and Sonny approaching.

'Yes,' said Claire, repositioning her glasses. 'Dr Moor was just telling us how constraint frustration can cause anxiety.'

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[1] Peled 2004
[2] Peled 2004

The two newcomers sat on an adjacent bench and looked attentive. ‘Please continue,’ said Sonny.

‘Another example,’ said Dan, ‘associates conflicting information processing with anxiety. Let us assume that a population of neurons processes certain information with an activation pattern relevant to that information. During the information processing, constraints among neuronal groups become satisfied in regard to the relevant information-dependent pattern of activity. Now imagine that another set of information is applied simultaneously to the system, however, this other information contradicts the original information. This pushes the system to an opposing configuration compared to the original information patterns. The result is that units in the system are simultaneously constrained to comply with opposing patterns of activity. Opposing patterns of activated units will disturb the process of constraint satisfaction taking place in the system, causing increased frustration to the constraint satisfaction processes among units in the system.’

‘Like being pulled in two directions at once,’ commented Sonny.

Dan nodded. ‘Assuming that anxiety is the emergent property from constraint frustration in the system[1], it is easy to understand why conflicting information processing increases the sensation of anxiety. Conflicting information processing involves experiencing opposing stimuli as well as confronting opposing actions in decision-making. In effect, our environment and our brain system are dynamically changing to provide continuous frustration on constraints, allowing for a continuous physiological life-long level of anxiety to characterize our psychic awareness.’

‘Then, a little stress is not a bad thing?’ asked Todd.

[1] Peled 2004

‘No, it’s how you deal with it,’ Dan replied.

‘Thanks again Dr Moor,’ said Rachel as they all stood.

‘Anytime,’ smiled Dan and waved as the four headed off across the grounds.

PART II: VALIDATION

Chapter 24

Dan arrived early at University Hospital and as he approached the main entrance he saw Helen speaking with a man around his own age. Helen waved Dan over to join them. She turned to the man and said, ‘This is Dr Moor, he will be able to help you.’

‘Good morning,’ Dan said with a smile.

‘Dan, this is Allan and he is writing an article about Validation tools, for a magazine. Do you have time to provide him with information?’

Dan turned to Allan. ‘You’re timing is perfect,’ he said. ‘I came early to sit in on one of Professor Krauss’s informal lectures. This morning he is talking about the history of the MRE. You can come with me.’

‘Excellent. Thank you,’ said Allan. ‘And thank you too,’ he said, turning to Helen.

‘You’re welcome,’ Helen replied. ‘If I wasn’t about to start my shift I would join you.’ She waved goodbye as she entered through the glass doors.

Dan turned to Allan. ‘There is an external entry to the room where the professor will speak,’ he said and led the way around the side of the building.

‘What, exactly, is an MRE?’ asked Allan as they walked.

‘MRE,’ said Dan ‘Stands for multiple reconstructive encephalography. It is the major tool for the Validation phase of mental disorders and the major corroborator to guide therapy processes. The MRE is a result of tremendous scientific effort over the last three decades.’

‘Really?’ Allan sounded surprised.

Dan nodded. ‘It reflects extraordinary developments within brain imaging technology combined with signal analysis. The MRE was developed in accordance with new ideas about mental disorders[1] that started to gain ground in the second decade of the century. When these ideas were applied to imaging and analysis results they started to make sense of the initially unclear, contradictory findings that characterized psychiatry imaging research of those days. The terms multiple and reconstructive reflect the combined integration of the different imaging modalities of the past within the MRE. The first modalities to be combined were functional magnetic resonance imaging—fMRI—and electroencephalography—EEG. This first combination was motivated by the complementary characteristics of these two imaging methods. fMRI had good spatial resolution and bad temporal resolution while EEG had a good millisecond range temporal resolution but a bad spatial resolution. As development of imaging technology proceeded, EEG and magnetoencephalography—MEG—were merged to give both electrical and magnetic samples of brain activity[2]. These were integrated with fMRI when problems of combining the MEG and the MRI magnets were solved[3]. Later, elements from single photon emission computed tomography— SPECT—and positron emission tomography— PET—were added to also enable imaging of long latency biochemical changes in the brain.’

They had reached an open door and entered a large room with ample seating. Professor Krauss was speaking with a group of students and he smiled when he looked across and saw Dan. He and Allan took seats towards the rear and for the next fifteen minutes an almost continuous stream of people entered the room and sat down. Allan readied his notebook.

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[1] Peled 2004
[2] Future 2018
[3] Future 2032

‘This must be a very popular topic,’ he said, looking around at the large audience.

‘Professor Krauss is an amazing man,’ said Dan. ‘Every session he holds is well attended,’ he added with a grin.

Professor Krauss moved to the front of the room and began speaking. 'The development of the MRE actually started with an explosion of imaging findings that increased markedly in the first years of the century. Pioneering work showed that left dorso-lateral prefrontal cortex—DLPFC—activation is involved directly in cognitive switching, in conjunction with parietal and temporal brain regions. It was also shown that pre- and postcentral gyrus activation was related to motor components of the switching set[1].'

Allan's eyes never left the professor as he began to pace slowly across in front of the listeners while he spoke. 'fMRI results revealed dissociable control processes in prefrontal cortex—PFC, with mid DLPFC selectively mediating resolution of response conflict and frontopolar cortex—FPC—further mediating subgoaling and integration. Anterior cingulate cortex—ACC—demonstrated a broad sensitivity to control demands, suggesting a generalized role in modulating cognitive control[2].'

Professor Krauss stopped pacing. 'The ability to bind information together, such as linking a name with a face or a car with a parking space, is a vital process in human episodic memory. To identify the neural bases for this binding process, brain activity was measured[3] during a verbal associative encoding task using event-related fMRI, followed by an associative recognition test for the studied word pairs. They found that encoding activity in bilateral anterior medial temporal lobe—MTL—regions was greater for successfully bound pairs. These findings provided evidence that the anterior MTL supported the successful binding of information in memory. Bilateral suppression

[1] Smith et al. 2004
[2] Badre and Wagner 2004
[3] Jackson and Schacter 2004

was detected[1], of the superior and middle temporal—auditory—cortex during visual working memory task and of the occipital—visual—cortex during auditory working memory task. This suggested that cross-modal inhibitory processes provide preferential access to high-order heteromodal association areas. Taken together, the findings suggested that although similar prefrontal and parietal regions are involved in auditory and visual working memory tasks, there were important modality differences in the way neural signals were generated, processed and routed during working memory tasks[2].'

A slight frown creased Allan's brow as he tried to understand what he was hearing. With his hands clasped behind his back, the professor began to pace slowly again. 'Using this knowledge about high-order normal brain functions, patients and their family members were assessed for brain imaging malfunctions. It was suggested[3] that relatives of persons with schizophrenia had subtle differences in brain function in the absence of psychosis. These differences added to the growing literature identifying neurobiological vulnerabilities to what was then called schizophrenia[4]. Later, evidence for a cortical-subcortical imbalance in this so-called schizophrenic brain was detected[5].'

The professor stopped pacing and continued speaking. 'Context processing was conceptualized as an executive function involved in voluntary, complex actions such as overcoming automatic responses. It was found[6] that in control subjects, left DLPFC activity increased when preparing to overcome an automatic response, whereas

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[1] Crottaz-Herbette
[2] Crottaz-Herbette et al. 2004
[3] Thermenos and colleagues
[4] Thermenos et al. 2004
[5] Abi-Dargham 2004
[6] MacDonald and Carter 2004

patients with schizophrenia showed no differential activation. In controls, context processing appeared to be associated with the differential representation of cues associated with the need to provide top-down support for overcoming automatic responses. This mechanism appeared to be impaired in patients with schizophrenia. The top-down control effect on body perception preventing a visual somatosensory illusion of position in normal controls was also shown[1]. In schizophrenia patients such control was weak, enabling a spurious reconciliation of visual somatosensory integration and a visual tactile illusion[2].'

While the professor was clarifying a point in response to a question, Dan looked across and noticed that Allan had taken few notes. He knew the reason when he saw the bewildered expression on Allan's face.

'A bit confusing?' asked Dan.

'Very,' replied Allan.

'Come with me,' said Dan as he stood. With a nod to the professor, Dan and Allan left the room. 'We'll go to the cafeteria,' said Dan, pointing the way. 'These talks are intended for students and staff, so can be a bit daunting if you are not familiar with the terminology.'

[1] Peled et al. 2003
[2] Peled 2004

Chapter 26

After getting drinks at the counter they sat down and Dan began to talk. 'Another part of the MRE is TOM—theory of mind, or mentalizing. It refers to the ability to attribute mental states to one's self and others. Inferring what people are thinking and feeling is an important aspect of human social interaction and requires a higher level of cognitive performance. At the start of the century, it was proposed[1] that such cognitive performance involved vast integrative abilities of distributed neuronal systems and high complexity of organizations in the global workspace or dynamic core[2].'

'Way back then,' muttered Allan, noting down the information.

Dan continued, 'These distributed neuronal systems have been documented with imaging studies since that time. A positron emission tomography—PET—study was conducted[3] to examine the neural substrates of TOM, using a task that mimics real-life social interaction. They found that TOM activated an extensive neural network that included certain areas of the brain[4] and most of these activations were limited to the left hemisphere, with the largest activation in two other specific areas[5]. A language-based TOM task activated distributed brain regions that are important for representing mental states of one's self and others, retrieving memory of personal experiences and coordinating and monitoring the overall performance of the task. The activations in the medial frontal cortex replicated findings in previous TOM studies.'

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[1] Peled 2004
[2] Edelman and Tononi 2000
[3] Calarge and colleagues 2003
[4] medial frontal cortex, superior frontal cortex, anterior and retrosplenial cingulate, and the anterior temporal pole
[5] contra-lateral right cerebellum and anterior vermis

‘This is great,’ murmured Allan as he continued taking notes.

Dan smiled to himself. ‘Functional magnetic resonance imaging—fMRI—was used[1] to investigate the neural correlates of person knowledge. Focusing on the neural substrates of action knowledge, participants reported whether or not a common set of behaviors could be performed by people or dogs. While dogs and people are capable of performing many of the same actions, such as run, sit and bite, it was surmised that the representation of this knowledge would be associated with distinct patterns of neural activity. Specifically, person judgments were expected to activate cortical areas associated with TOM reasoning, whereas action-related judgments about dogs were associated with activity in various regions[2]. Identical judgments about people yielded activity in specific areas[3]. These findings suggest that person knowledge may be functionally dissociable from comparable information about other animals, with action-related judgments about people recruiting neural activity that is indicative of TOM reasoning.’

‘It’s incredible that this activity can be pinpointed,’ said Allan. ‘If that took place at the beginning of the century, what has happened since then?’

[1] Mason et al. 2004
[2] including the occipital and parahippocampal gyri
[3] prefrontal cortex, notably the right middle and medial frontal gyri

'Well,' said Dan, 'in the 2000s, the amount of data about brain activations using fMRI, electroencephalography—EEG—and magnetoencephalography—MEG—reached colossal dimensions in quantity as well as quality. Virtual reality technology—VRT—was used to upgrade the complexity of additional stimuli for imaging cognitive challenges. However, the diversity of results and methods made it difficult to extract useful information from these studies. More importantly, there was no applicable theoretical framework to form a working context within which to explain these findings. At the same time, the work of authors[1] laid the ground for a system approach to the data collected but it was only later, when different authors[2] started to integrate imaging data with system approach, that meaning began to emerge from the studies. This integrative approach was also influenced by the theoretical work of a number of authors[3] as well as practical work by another[4].'

The sound of familiar voices caught Dan's attention and he turned towards the source. The four young students he had met the day before were at the counter. He waved to them and they headed in his direction, sitting at the table next to Dan and Allan. Dan made the introductions and told them Allan was writing an article on MRE and he was giving him information.

'We have covered some of that,' said Clare. She positioned her glasses and picked up her drink.

'Signal analysis techniques that could identify breakdowns in the systems and disturbances to neuronal ensembles and their functional organization were beginning to develop,' said Dan.

[1] Friston 1998; Tononi 1998; Breakspear 2004; and others
[2] Future 2011
[3] Such as Tononi 1998; Edelman 2001; and Peled 2004
[4] Friston 1996

‘EEG for example?’ suggested Sonny.

With a smile, Dan said, ‘Scalp EEG signals are produced by partial synchronization of neuronal groups across areas of the cortex, in a centimeter-square grid. This synchronization optimizes relations between spike mediated neuronal communication, both between and within brain areas. Traditional analysis of event-related EEG data was done either in the time or the frequency domain approaches.’ Allan’s brow creased.

‘May I?’ asked Todd. Dan nodded. ‘In the time domain approach, researchers averaged a set of data trials, or epochs, time-locked to some class of events. This yielded an evoked response potential—ERP—waveform at each data channel.’

‘The frequency domain approach,’ interjected Sonny, ‘averaged changes in the frequency power spectrum of the whole EEG data, time-locked to the same events. This produced a two-dimensional image called event-related spectral perturbation[1].’

‘In order to combine EEG with imaging techniques,’ said Rachel, ‘Source localizations of EEG activity were required.’

Allan looked at Dan, who explained, ‘At the beginning of the century, some crude calculations offered certain current density estimation techniques. These were devised to explain three-dimensional intracerebral activities. They were also attempts to solve the inverse problem, which was a mathematical problem of projecting back the EEG data to locate its source within the head. From these techniques low-resolution electromagnetic tomography—LORETA—gained certain credence at the beginning[2]. It did not require the assumption of a specific

[1] Makeig et al. 2004
[2] Pascual-Marqui et al. 1994

number of sources, as in dipole source localization. Instead, it adapted the assumption of smoothest constraint.'

Allan's brow creased slightly. 'That means,' elaborated Claire, 'that for any given discrete point in the brain, the current density should be as close as possible to the average current source density of its closest neighbors. By applying a Laplacian operator to the current density, the spatially smoothest current distribution could be determined[1].'

'With this assumption,' continued Dan, 'A particular current density distribution can be singled out among the infinite number of solutions, which is the answer to the inverse problem.'

'I didn't realize the MRE was so involved,' said Allan, shaking his head.

'There's more,' advised Rachel with a grin.

Allan blinked and said, 'I'm ready.' All eyes turned to Dan.

[1] Mulert et al. 2004

'Statistical parametric mapping was the basis for MRE development,' he said. 'It referred to the construction and assessment of a spatially extended statistical process used to test neuronal hypotheses about imaging data from SPECT, PET and fMRI.'

'The statistical parametric mapping approach was voxel based,' said Sonny.

'Voxels are represented by pixels in the display and the imaging,' explained Rachel.

Allan nodded as Todd said, 'The images are spatially normalized into a standard space and smoothed.'

Dan was impressed by the student's knowledge on the subject. 'Parametric statistical models are assumed at each voxel,' he said. 'The general linear model was used to describe the variability in the data, both in terms of experimental and confounding effects, and residual variability. Hypotheses expressed in terms of the model parameters are assessed at each voxel with univariate statistics.' Allan seemed to be following the information so Dan continued. 'This gives an image with voxel values that are statistics, a statistic image or statistical parametric map[1]. Temporal convolution—time manipulation—of the General Linear Model for fMRI enables the application of results from previous tests to be serially correlated, permitting the construction of statistic images from fMRI time series.'

'Wouldn't that be difficult to sort out?' asked Allan.

Dan shrugged. 'The multiple comparisons problem of simultaneously assessing all the voxel statistics,' he replied, 'is solved by using the theory of continuous random fields. This is assuming that the statistic image is a good lattice representation of an underlying continuous

[1] SPM{t}, SPM{Z}, SPM{F}

stationary random field. Results for the Euler characteristic lead to corrected p-values for each voxel hypothesis. Also, the theory permits the computation of corrected p-values for clusters of voxels exceeding a given threshold, as well as for entire sets of supra-threshold clusters, leading to more powerful statistical tests at the expense of some localizing power[1].'

'Sounds very complicated to me,' confessed Allan.

'At first,' said Todd, 'The combined fMRI and EEG findings were united using reference systems such as the Talairach space, which was extracted from brain dissections and photographs for the Talairach atlas.'

Allan turned to Dan for clarification. 'The Talairach space was a representative brain of the population calculated from 241 normal MRI scans. The method of combining the distinct imaging data on this space used smoothing, adapting, converging and three-dimensional regression techniques[2].'

Allan nodded and Dan continued. 'It wasn't only imaging localizations that were of interest in those early days of imaging,' he said. 'Other modes of signal analysis could provide valuable information on brain organization. Blind source separation, for example. The term blind indicated that the signals, which cannot be measured directly and about which we have little or no information, were isolated from measurements of mixtures of them. It was also known as the cocktail party problem.'

'That's because,' said Rachel, 'it's very much like a number of people talking in a room while a number of microphones record the sound in the room.'

'The sounds recorded by each microphone represent a weighted mixture of all the people's voices,' said Sonny. 'The weights depend on the microphone location in the

[1] Kiebel and Friston 2004
[2] Mulet et al. 2004

room and the problem is to extract each single person's voice from the total sound the microphones have recorded.'

Dan nodded. 'Much in the same way, an EEG or MEG reading is of the head surface distribution of the total magnetic field as recorded by N sensors distributed over the subjects head,' he said. 'The scope is to differentiate the independent sources that contribute to the EEG signal. The application of this independent component analysis—ICA—to MEG and EEG data assumes the existence of signal sources statistically independent from each other, that the mixing of their contributions is instantaneous and linear, and that both the source signals and the mixing process are spatially stationary. Independence may seem difficult to assume with simultaneously active brain sources, but the concept of independence was referring to the statistics of their amplitude distributions and not the physiology of the neural sources.'

Allan was taking copious notes. He stopped and looked at Dan. 'Is there more?' he asked.

Dan nodded. 'Event-related changes in power and phase consistency across single trials time-locked to experimental events characterized event-related perturbations in the oscillatory—fluctuating—dynamics of ongoing EEG signals.'

'Combining ICA with these event-related changes,' said Todd, 'avoided the problems caused by positive and negative potentials from different sources canceling each other out at the recording electrodes.'

'And,' added Sonny, 'it also prevented the misallocation of activity, which originates in various and often distant cortical sources, to the recording electrode.'

'If the activity of different EEG components were relatively independent of one another,' said Dan, 'their local field activities must be largely separated physiologically. Under favorable circumstances, ICA should separate EEG and MEG data into physiologically and functionally distinct sources. ICA minimized the influences of volume conduction and identified the activities of individual cortical sources. Their oscillatory dynamics were more physiologically plausible, more tightly linked to behavior, and amendable to trial-by-trial analysis.'

Clare looked down at her watch. 'We have to go,' she said, pushing her glasses back up.

'Lecture,' said Rachel by way of explanation as they collected their things.

'A lot of work has gone into developing the MRE,' said Allan as they watched the students depart.

'There is even more but I'm sure you have enough background for your article,' said Dan. 'However, I will tell you about the MRE itself.'

'MRE is not a passive imaging modality equal to all patients,' began Dan. 'In a sense, it is a direct continuation of the Investigation phase because the cognitive challenges applied during the MRE were determined by the results of Investigation. The virtual reality scenarios—VRSs—that are applied to challenge the patients cognitive capabilities are determined by the hypothesis reached by the psychiatrist in the Investigation phase. Specifically tailored, predetermined VRSs are applied by the psychiatrist to each MRE examination. There are four VRS modules in the MRE. One is MI-VRS, meaning multimodal integration virtual reality scenario. Two is TOM-VRS, meaning theory of mind virtual reality scenario. Three is EI-VRS, meaning exploration and intervention challenging virtual reality scenario. And four is PS-VRS meaning psychosocial virtual reality scenario.'

Allan looked up from his notes. 'What is the difference between the scenarios?' he asked.

Dan sat forward and crossed his arms on the table. 'The MI-VRS,' he began.

'Multimodal integration VRS,' interjected Allan.

Dan nodded. 'Involves an environment that challenges all of the brain modalities, that's auditory, visual, motor and so on, at the same time. Built into this VRS are challenges to simple-level reflexive integrations between brain modalities that also challenge additional higher-level integrations. Memory and working-memory multimodal functions, as well as concentration requirements, are also built into this VRS module. An MI-VRS could be navigation in an office building or mall, where orientation and progression depend on visual motor coordination, such as avoiding bumping into the virtual walls or virtual furniture, or it might depend on auditory visual integration, which could be opening doors according to a specifically combined visual and auditory cue, a certain color or shape button emitting a specific bell sound. Working memory is challenged in this VRS module when progression through successive doors depends on remembering codes of previous doors. Time lags between one door and the next door require the subject acting in this VRS to hold in memory the combined auditory and visual combined cues of the previous door to be able to open the next door. In such a way multimodal working-memory is challenged.'

Allan nodded. 'And the second type, theory of mind VRSs?' he queried.

'TOM-VRSs are scenarios within the virtual environment that require the subject to perform using theory of mind skills. Typically, this involves virtual acting persons, which are also termed avatars in VR language. Performance in this type of environment will be accomplished only if the subject acting in that environment can foresee what other person's—avatar's—intentions are and respond appropriately, based on predicting their intentions.'

Allan continued adding to the extensive notes he had already taken.

'EI-VRSs,' said Dan and waited for Allan to respond.

'Exploration intervention VRSs,' expanded Allan.

Dan suppressed a smile. 'Involve exploring new environments, typically the inside of a home or apartment in which there are many rooms and interesting objects,' he said. 'The subject in this VRS can explore the house and may also intervene and change the scenarios by moving things around, re-organizing the furniture and so on. The extent of exploration and interventions are monitored to give an idea of the interest and activity levels of the tested subject.'

Nodding, Allan asked, ‘And the last one, the psychosocial VRSs?’

‘PS-VRSs,’ said Dan, ‘are sets of social interpersonal situations referring to the person being examined. In these scenarios, the subject’s interpersonal psychological reactions are investigated and sampled. For example, a party with attractive persons could attract a person with a personality that was once called narcissistic. However, if one or more of the avatars become critical toward the subject then the person would tend to disengage from that virtual situation. Measurements of references to predetermined psychosocial situations can screen personality tendencies as they are expressed in interpersonal relationships. With MRE, state-space dynamics and optimization dynamics can readily be assessed during PS-VRSs.’

‘Do all patients have the same scenarios?’ asked Allan.

Dan shook his head. ‘The four VRS modules are combined in various portions to form the total VRS applied to the MRE. If equal portions of each type of VRS are desired then each VRS contributes 25% to the total VRS. Based upon the Investigation results, the psychiatrist decides the different proportioning of the VRS contents. For example, to create a VRS that has equal portions of each VRS module, the psychiatrist codes the request as MI=0.25, TOM=0.25, EI = 0.25 and PS=0.25.’ Dan thought of what he had coded for Steve; MI=0.5, TOM=0.4 and PS=0.1. This was because of the Investigation hypothesis, which assumed dynamic core fragmentation, modality disconnection and hierarchical breakdown. ‘The MI and TOM are the major VRSs for assessing the global dynamic integrations. Also, the TOM-VRS module is useful for the assessment of hierarchical organizations.’

‘Each scenario,’ said Allan ‘Is tailored to suit the patient?’

‘Yes,’ replied Dan. He looked at his watch and stood as he said, ‘I’m afraid I must go to the ward now.’

‘Thank you,’ said Allan ‘For your time and all the information. It is extremely interesting.’

They parted company in the corridor and Dan headed in the direction of the ward to see if any of his patient’s results had arrived. His thoughts on signal analysis continued as he walked.

He recalled that more sophisticated nonlinear methods to estimate EEG signals were also developed at the start of this century. Dimensional complexity of an EEG signal was found to measure certain conscious mental states. With increased depth of sleep, the dimensional complexity of the EEG decreased. An algorithm was published[1] to estimate the correlation dimension D2, which was first used for EEG analysis[2]. This method of analysis was found to be sensitive to the psychophysiological states of sleep. Estimations of change in dimensional complexity from baseline to cognitive challenge were found. Some[3] argued that the direction of the change was related to the position of the particular electrode. They thought that for brain regions that were less involved in the task, dimensional complexity increased, while for those regions engaged in the specific processing, dimensional complexity decreased. These assumptions were replicated[4] and found that during working memory tasks that challenged frontal brain regions, electrodes from frontal scalp regions showed decreased dimensional complexity while other scalp electrodes remained at a higher level. Dimensional complexity estimations were the preliminary algorithms of what would later become one of the important contributions for estimating the organization level and extent of the dynamic core[5].

‘Penny for them,’ said a voice, bringing Dan out of his reverie. He turned to see Helen keeping pace with him.

Dan stopped. ‘Pardon?’ he said.

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[1] Grassberger and Procacia (Gregson et al. 1993)
[2] Babloyantz and Destexhe 1986
[3] Elbert et al. 1994
[4] Sammer 1999
[5] Future 1024, 1025; Future 1027

‘It’s an old saying, ‘‘A penny for your thoughts’’,’ said Helen.

‘Ah,’ said Dan. ‘I was thinking about signal analysis techniques.’

‘If you are going to the ward,’ said Helen ‘You can enlighten me on the way.’

Dan nodded and they began walking again. ‘All of the signal analysis techniques set the basis for direct generative models of cortical dynamics, which involved realistic, multi-scale finite-element modeling of field activities,’ said Dan. ‘These realistic whole-brain neural network models contained samples of the information about the states of the brain. Then, based on realistic algorithms of brain organization, simulated the specific individual-dependent brain dynamics and displayed this as output evaluations of the specifically studied brain activity.’

‘It must have taken quite some time to perfect that,’ commented Helen.

‘Simulation algorithms were already widely existent at the start of the century,’ replied Dan. ‘It was works[1] published in neural network journals in 2001 that laid the ground for simulating brains more accurately. Intracellular recordings and imaging experiments have previously revealed the widespread existence of repeated dynamics in spontaneous activity of neocortical circuits in vitro and vivo.’

‘Repeated dynamics in the lab as well as in living organisms,’ mused Helen. ‘Wouldn’t the dynamics be difficult to pick up in either case?’

Dan shook his head. ‘The detection of these dynamics was made easier by the ability to reconstruct the activity of a large population of neurons, as well as the increased statistical power of correlating intracellular

[1] Such as that by Sommer and Wennekers

records rather than spikes. These repeated patterns were found to be robust.'

'In what way?' asked Helen.

'A number of ways,' answered Dan. 'Not only did they occur more frequently than expected by chance, but they can happen at the same time in two neurons, occur simultaneously in intracellular and optical recordings, and are correlated with intracellular state depolarization and network synchronizations. These repeated neuronal patterns involve circuits with structured topographies, from modular patterns with compressed timing, and were found to be blocked by antagonists of relevant neurotransmitter receptors. These findings demonstrated that stochastic cortical synapses could work with high reliability to produce stereotypical dynamics that are reduced in dimensional space.'

They had reached the ward and stopped at the nurses' station. Dan continued speaking. 'Higher order grammar has explained how sequences of neuronal activations with high temporal precision of firing, also termed synfire chains[1], can be modules of larger temporal structures, global dynamics. They are defined by their sequential order of activation and can last for minutes, sustaining global brain organizations for long intervals of time.'

'Synfire chains?' queried Helen.

'These synfire chains have compressing dynamics,' said Dan. 'It's as if their circuit was replaying and modifying previously learned sequences from which the neocortex could spontaneously generate precisely reverberating temporal patterns of activation dynamic ensembles, and that these could represent growing building blocks of cortical function.'

'Very interesting,' said Helen.

[1] Aviel et al. 2003

‘These insights,’ continued Dan, ‘led to awareness of how the brain dynamically works in healthy conditions and in disturbed circumstances. They also allowed for simulations that were later used to represent higher-level dynamic imaging of the MRE.’

Helen moved behind the desk. ‘I’ll see if any results have come in for you Doctor,’ she said. She opened a file and handed the information to Dan.

‘Thank you,’ said Dan looking down at the SCEsystem results obtained from Steve’s earlier evaluation. The results confirmed that Steve’s speech patterns support state-space fragmentation as well as a certain tendency toward reduced periodic attractors and local minima—the tendency to get stuck in certain contents.

‘That’s all there is for you at the moment,’ announced Helen. ‘The MRE results are not in yet.’

‘I’ll go to the MRE department and check on the progress of the tests,’ he said. He waved as he wandered off down the corridor.

Approaching the staff lounge, Dan decided he had time for a drink before going to the MRE department. He was pleasantly surprised to find Professor Krauss having a coffee break.

‘Ah, my young friend,’ said the professor. Dan explained about Allan and their early departure from the professor’s talk. ‘Yes,’ said Professor Krauss. ‘I can see how it would have been a little overwhelming for him. What are you up to now?’

‘I have been thinking about neural network models,’ answered Dan. ‘Developed in the 80s and 90s of the previous century, they were simplified representations of neurons, having input summation and threshold-dependent output.’

‘Yes,’ said the professor. ‘The units were richly interconnected to resemble the massive synaptic connectivity found in neural tissue. These models abstract from the complexity of individual neurons and the patterns of connectivity in exchange for analytic tractability. Independent of their use as brain models, they were being investigated as prototypes of new computer architectures. Some of the lessons learned from these models can be applied to the brain and to psychological phenomena[1].’

‘As I recall,’ said Dan, scratching his head, ‘one of the relevant models was the class of feed-forward layered network with added feedback connections.’

‘In the feed-forward layered network architecture,’ detailed the professor, ‘information was coded as a pattern of activity in an input layer of the model neurons. This was transformed by successive layers receiving converging synaptic inputs from preceding layers. Added feedback connections transform the architecture of the network to a

[1] Rumelhart 1986

fully interconnected structure also termed after its inventor, the Hopfield network. In the Hopfield model, learning was achieved by adjusting or strengthening connections between the units to strengthen certain activation patterns in the model. Strengthening connections simulated synaptic plasticity and the Hebbian algorithm in the model determines higher activity to the units more strongly connected.'

'Input was in the form of an initial pattern of unit activation distributed over all of the units,' said Dan. 'The units in the model were then left to interact with each other. Due to the predetermined strengthening of connections, the model tended to activate the pattern that was closest in configuration to the input pattern.' He went over to make himself a cup of coffee.

The professor leaned back and clasped his hands behind his head. 'The distance between the input pattern and the activated pattern was measured in terms of hamming distance,' he said. 'This reflects the number of units with different activation values between the two patterns. In that manner, the Hopfield model achieved a computation of content-addressable memory activation.'

Dan sat down. 'The pattern strengthened by connection encodes the memory,' he said, 'just as Hebbian dynamics probably determines learning in real brains. And the input activates the relevant associated—nearest in hamming distance—memory.'

The professor nodded. 'As one memory is associated with its relevant remainder. The content-addressable computation has been successfully applied to problems of isolating features and recognition of visual and other stimuli, therefore simulating brain perception and perception-dependent memory activation[1].'

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[1] Rumelhart 1986

‘It amazes me,’ said Dan as he sat down, ‘that this rich and advanced knowledge of brain dynamics was available to psychiatrists for so many years, starting in the 80s of the previous century up to the 2000s of this century, and psychiatrists failed to make use of it to revolutionize psychiatry much earlier than it finally came about.’ Dan shook his head.

Professor Krauss looked at the ceiling as he spoke. ‘A short manuscript[1] from 2004 was one of the predecessors in this direction. It not only applied the knowledge of modeling brain dynamics to psychiatric disorders but also allowed for previously incomprehensible findings in brain imaging of mental disorders to become understandable under new formulations. The disturbance that was previously titled schizophrenia—now rightly named neuronal complexity breakdowns—had confusing misinterpreted findings in nearly all of the imaging studies of that time.’

‘Yes,’ said Dan, pensively. ‘There was a debate about hypofrontality—low activity in the front of the brain—in schizophrenia. Hypofrontality was the most replicated finding in schizophrenia. Up to the first years of this decade it was a relatively less dorsolateral prefrontal cortex function, especially when schizophrenics were engaged in a frontal lobe task such as the Wisconsin card sorting task.’

‘However,’ said the professor, looking at Dan, ‘additional studies from that time did not replicate these findings and found greater dorsolateral prefrontal cortex activation in these patients[2]. Later, areas of both greater and lesser dorsolateral prefrontal cortex activations were found[3] in schizophrenia patients compared to healthy subjects performing the same task. It was realized that neither

[1] Peled 2004
[2] Curtis et al. 1999
[3] Callicott and colleagues 2003

hypofrontality nor hyperfrontality was a sufficient explanation for working memory deficits in schizophrenia. It was assumed, and was later identified within multiple constraint connectivity breakdowns[1], that patients possess an abnormal neuronal strategy and handle working memory information differently to healthy comparison subjects.'

'That was not the end of conflicting findings though, was it?' prompted Dan.

Professor Krauss shook his head. 'Using dimensional complexity measurements of EEG in schizophrenia patients showed[2] a higher dimensional complexity under resting conditions, as well as task conditions, compared to healthy control subjects. The results were interpreted in terms of the looseness of thoughts in schizophrenia. Previous research[3] also found a higher dimension of the resting EEG in schizophrenia patients at a frontal electrode position. But in contrast, found a lower dimension at central electrode locations compared to normal control subjects. These findings were interpreted as reflecting the dissociation of EEG activity in schizophrenia patients compared to coupled processes in normal subjects.'

Dan looked thoughtful. 'The results from analyzing the sleep EEG of schizophrenia subjects were also contradictory.'

'True,' said the professor. 'A decrease of the D2-dimension was found in the EEG of schizophrenia subjects during sleep state II, as well as during rapid eye movement—REM—sleep, compared to healthy subjects. However, an increase of the complexity in the EEG of schizophrenic patients was found during REM sleep, estimating the first principal Lyunouv exponent, a measurement of divergent degree of a nonlinear system

[1] Peled 1999
[2] Koukkou et al. 1993
[3] Elbert et al. 1992

dynamics. The findings of these dimensional complexity measurements gave no clear reliable picture about the EEG brain-dependent organization. The confusion was attributable to the fact that schizophrenia was not a homogeneous entity and what were measured were different breakdown patterns of brain organizations. Only the initiation[1] of a reformulation of schizophrenia as a brain dynamic disturbance made it possible to reinterpret the findings into a meaningful result.'

'All those contradictions in the findings,' said Dan, 'must have been exasperating for the researchers.' The professor nodded in agreement.

Dan got up and took his cup to the kitchen. Looking across the bench he noticed some information sheets about MRE. Picking one up, he turned to the professor and held it out. 'Allan might be interested in this,' he said. 'I'll pass it on. Now I must go to the MRE department and see if my patients' results are ready.'

'Ah,' smiled Professor Krauss. 'The proof to support your diagnosis.'

Dan grinned and waved as he left the room. Realizing he still had the sheet in his hand, Dan began reading it as he made his way through the hospital.

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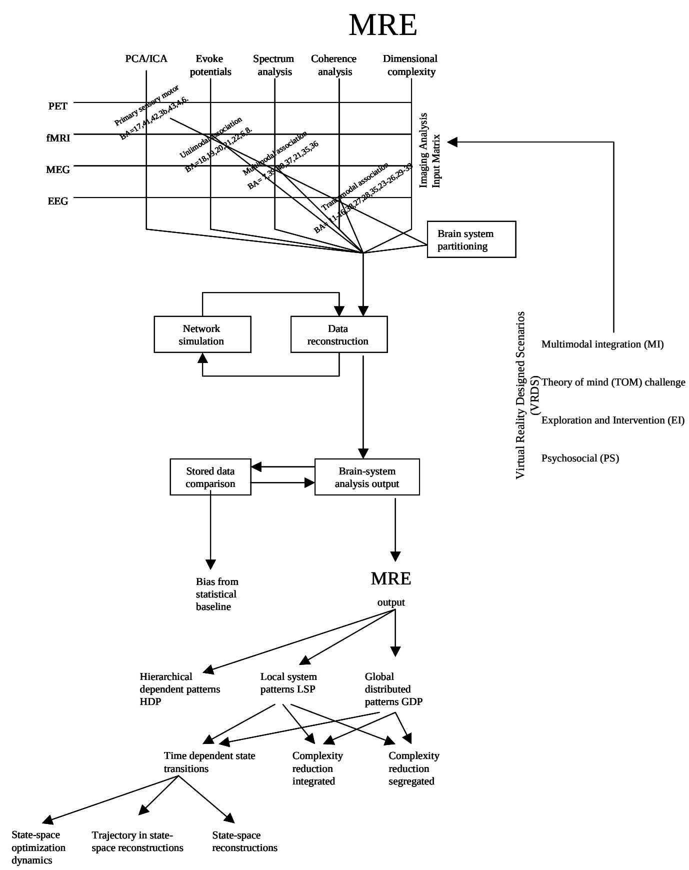
[1] Peled 2004 and others

The MRE uses an imaging analysis input matrix—IAIM—as the basic data set for investigating brain dynamics (figure 1). The matrix represents online parallel jointly sampled imaging data from fMRI, MEG, EEG and PET, which is test-dependent and not always used. The IAIM also uses online combined multiple analyses methods including ICA, coherence, evoked potentials and dimension complexity analyses.

Figure 1: MRE



The data is applied to the whole brain as well as to a partitioned brain divided into specific multiple brain regions and systems. Partitioning is achieved according to described[1] brain organization systems, with unimodal, multimodal and transmodal systems hierarchically considered. Due to multiple inputs from numerous imaging modalities, conversion regression and smoothing techniques are needed to enable good estimations of brain activity during mental functions.

The activity data is further evaluated through combined feedback processing of neural network simulations and data reconstruction. These processes makes it possible for the imaging data, initially limited to certain time points and instances of brain activity, to be further reconstructed to include time-dependent state-dependent brain activity spread over time. In essence these are simulations of large-scale brain functions deduced by neural network modeling from the basic data of the IAIM.

The outcome of such processing, called brain-system analysis output—BSAO—is compared to accumulated and updated epidemiological-dependent data, forming a statistical background called stored data comparison—SDC—module. The SDC assesses to what extent the individual being evaluated differs, or biases, from statistically common brain activity. This information is particularly important to evaluate degrees and severities of disturbances.

The MRE output is arranged to assess global as well as regional brain organizations. For example, the neural complexity can be estimated for whole brain as well as for hierarchically partitioned brain. The patterns of connectivity, integrations versus segregations, when assessed globally, regionally and hierarchically provide for a reasonably accurate assessment of brain organizations.

[1] Mesulam 1998

A more complicated and computation-demanding assessment involves the reconstruction of state-space dynamics. These are the calculations that require tremendous simulation power. Neural network models that have realistic structure, as well as real individual-dependent inputted imaging data, can reconstruct the dynamics of the specific brain under examination and make a close estimation of that individual's state-space configurations and trajectory dynamics. Such reconstruction is extremely complicated and uses both global as well as partitioned brain evaluations.

Comparing the dynamic changes over time allows for calculation of optimization dynamics. If the system moves from larger to smaller Hamming distances between instant statistical configuration and state-space configurations then it is said to optimize these configurations. The opposite is also true for deoptimization dynamics, when the system moves from smaller to greater Hamming distances.

Dan arrived at the MRE section and was handed the test results, which included all samplings, simulations and calculation algorithms.

‘Is there somewhere I can read through these?’ Dan asked the nurse.

‘One of those consultation rooms should be vacant,’ said the nurse, pointing to several doors across the corridor.

Dan knocked on the first door and, receiving no reply, opened it. He sat down and looked at the results. Typically, Dan’s first interests were the summaries and end points of the validation.

Steve’s results were first and showed that Steve had a major neural complexity reduction in global distributed patterns. Dan could see that it was the disintegrated type of neural complexity reduction. Also, local systems patterns suffered from the same complexity type of reduction, especially the frontal region systems[1]. Hierarchical imbalance was reflected in Steve’s MRE by instability over time of hierarchical-dependent patterns. Hierarchical insufficiency was identified in the MRE by comparing transmodal neural complexity measures of prefrontal region systems, in respect to lower level multimodal and unimodal systems. Dan noted that these were relatively disorganized, making them non-functional as top-down processes and leaving the global brain organization deprived of higher-level computations.

Dan ran his fingers through his hair as he formulated his Intervention plan for Steve. When he was satisfied, Dan looked at the next set of results.

These were Tim’s results and, as expected due to loss of frontal-lobe tissue, Tim’s MRE results showed more clear-cut hierarchical imbalance. In this case a static

[1] hippocampal and parietal systems

imbalance, since all transmodal activity was lost due to the damage to the frontal cortex. Global brain organization was fragmented, with each subsystem continuing to maintain a certain neural complexity level that deviated only mildly from standard statistics.

Dan knew that depending on input loads, synchronized discharges could emerge as global synchronized activity, accompanied by attacks of restlessness, rage, and disorientation. These discharges were similar to epileptic seizure synchronization but on a higher-order of coherence pattern than the regular first-order plain electrical synchronization evident in epilepsy. This higher-order coherence pattern activity was enough to show the instability of the brain system when deprived of its major organizer and moderator of top-down transmodal activity.

In many ways this loss of top-down transmodal regulation was similar to Steve's pathology. It has been known for decades that in effect, the clinical pictures of frontal lobe syndromes and certain phases of what was once called schizophrenia typically overlapped. Tim was investigated for MRE results using the VRS codes: MI-VRS = 0.5 and TOM-VRS = 0.5, based on the assumption that personality problems in Tim's case are secondary to the brain damage.

After reading Tim's MRE results, Dan made a note to order brain tissue for transplantation in Tim's brain. The tissue order was estimated by parameters dictated by MRE measurements of neural tissue volumetric losses and cultivated from specific stem cells. These stem cells—ES cells—are multipotent progenitors with unlimited developmental potential. Different ES cell-derived neuronal progenitors, cultured in the laboratory, can develop into functional neurons when transplanted in the central nervous system.

There was a tap on the door and Dan looked up at the nurse standing there. ‘Hello,’ he said.

She smiled and entered the room. ‘These just came in,’ she said as she handed more results to Dan.

‘Thank you,’ said Dan as she turned and left. Dan looked down and saw that they were Pamela’s test results. Now that he had results for all of his patients, Dan decided to return to the staff lounge.

Stepping out of the room, Dan noticed Helen walking ahead of him. He quickened his pace to catch up with her. ‘We meet again,’ he said as he came up beside her.

Helen stopped and turned to him. ‘You startled me.’

Dan raised his eyebrows and suppressed a grin. ‘What are you doing down here?’ he asked as they began walking again.

‘I escorted a patient down for tests,’ answered Helen. ‘He has a severe head injury.’ She shook her head briefly and turned to Dan. ‘I know very little about transplants.’

‘If you are going back to the ward,’ said Dan ‘I can give you some background information.’ Helen nodded.

Chapter 34

'As early as the beginning of the century,' Dan began, 'there were investigations into the effect of treatment with specific neurospheres and bone marrow-derived stromal cell spheres in rats with traumatic brain injury—TBI. The transplanted composite was injected into the TBI contusion site 24 hours after injury and investigated on Day 14 after transplantation. The Rotarod test and the neurological severity score were used to evaluate neurological function. The transplanted tissue was analyzed in recipient rat brains by using histological staining and laser scanning confocal microscopy. The lesion volumes in the brains were also calculated using computer image analysis. Rats that received the transplants had reduced lesion volume and showed improved motor and neurological function when compared with control groups 14 days after the treatment. These results suggested that transplantation of specific neurospheres and bone marrow-derived stromal cells may be useful in the treatment of TBI[1].'

He exchanged looks with Helen and continued. 'That same year, other researchers[2] injected neural stem cells—NSCs—derived from the germinal zone of E14.5 GFP-expressing mouse brains that were cultured as neurospheres in FGF2-enhanced medium, into the injury cavity in rat brains. They managed to show that FGF2-responsive NSCs present a promising cellular therapy following trauma and that the transplant location and environment may play an important role in graft survival and integration.'

Dan thought for a moment. 'A couple of years later, low densities of undifferentiated mouse specific stem cells—mES cells—were grafted[3] to adult mouse brain

[1] Lu et al. 2002
[2] Tate and colleagues 2002
[3] Harkany and colleagues 2004

regions associated with neurodegenerative disorders. This demonstrated that ES cell-derived neurons undergo gradual integration in recipient tissue and acquire morphological and electrophysiological properties indistinguishable from those of host neurons. It was also shown that only some brain areas permitted survival of mES-derived neural progenitors and formed instructive environments for neuronal differentiation and functional integration of naive mES cells. The region-specific presence of micro-environmental cues and their pivotal involvement in controlling ES cell integration in adult brains stressed the importance of recipient tissue characteristics in formulating cell replacement strategies for neurodegenerative disorders.'

'I didn't realize there was transplant research going on as early as the start of the century,' stated Helen.

Dan nodded. 'This early century pioneering work developed what later became transplanted brain plasticity inducers—BPIs. It is currently possible to graft specific stem cells, derived from progenitor cells and cultured in the laboratory, which have been differentiated into functional neurons specifically matched to every brain region and structure. These transplants are then induced by specific growth factors and neuro-hormones[1] to migrate, make connections and function within their relevant neuronal networks in the brain. The transplanted BPI is reserved, together with the electrical BPI treatment, for severe brain damage with loss of neuronal tissue, as in the case of my patient, Tim. As a final preparation before operation, the transplant itself is subjected to the activity of a microelectrode grid that injects electrical currents, as well as samples electrical neuronal activity. In this state, the system can be induced to organize synaptic connections in a way that neural complexity is increased in the system

[1] Future 2019; Future 2023

before it is subjected to the neuronal influences after transplantation.'

They reached the entry to the ward and stopped. 'Very interesting,' said Helen. She flashed Dan a smile and walked briskly in the direction of the nurses' station. Dan stroked his chin thoughtfully then went to check on his patients.

Chapter 35

Dan opened the door to Steve's room and saw him sitting on the side of the bed, facing the wall opposite the door. Dan walked around the bed so that he could see Steve's face and let him know he was there. Steve seemed to be completely oblivious to Dan's presence. There was no expression on his face and occasionally he would give a short nod, as though listening to someone speak. Dan watched him for a short time and then quietly left the room.

The door to Tim's room was open and the light was off when Dan arrived. He stood in the doorway and there was enough light coming through from the corridor for him to see that Tim was sleeping. The slow, even rise and fall of his chest suggested Tim was very relaxed. Not wishing to disturb him, Dan turned and left. Tim's family had been so upset by his condition that they could not bring themselves to come to the hospital, preferring to telephone the ward regularly to check on Tim's condition. Dan made a mental note to call them tomorrow to discuss Tim's treatment.

Pamela's eyes were closed when Dan entered her room. As he took a step towards the bed, her eyes opened.

'Hello Doctor,' she said.

'Hello Pamela,' said Dan smiling. 'How do you feel?'

'A little better now that tube has been taken out,' said Pamela, wincing at the thought.

'Good,' said Dan, smiling broadly. 'Now all we need to do is cheer you up.'

Pamela managed only a brief, pathetic smile in return.

'Try to get some sleep,' said Dan. He gave her one last smile and went out the door.

Back in his office, Dan sat down at the computer and began ordering the first initial steps for the optimization program to be taken in the Intervention phase of Steve's and Tim's therapies. After he ordered neural transplant tissue and the different brain plasticity inducers, Dan looked at Pamela's results.

Her MRE was totally different to Tim's and Steve's. He had coded her VRS as MI=0, TOM=0.05, EI=0.05 and PS=0.9. Pamela's MRE results concentrated on findings pertaining to time-dependent state transitions, while neural complexity and hierarchical balances of brain systems were no different from normal subjects. State-space and trajectory reconstructions were the major targets for investigation using the MRE and they revealed frequent deoptimization dynamics. These deoptimization dynamics were phased-locked to specific psychosocial—PS—events within the VRS during the MRE process. The reading of these PS events within the VRS amounted to few themes, all having in common a message of rejection or criticism within a psychological interpersonal context.

Dan sighed and ran his hand through his hair, then turned back to the computer to complete the ordering process for the Intervention phase.

PART III: INTERVENTION

Chapter 36

Dan arrived at the hospital with mixed feelings. Today he was due to give his first student lecture on the topic of treatment modalities within the optimization process. While he was confident in his knowledge, the prospect of speaking to a large group of students was a little daunting.

Dan stopped at the open door to the lecture room and surveyed the audience. He was both pleased and anxious to see that the room was full. He ran his hand through his hair and strode purposefully to the front of the room and faced the students.

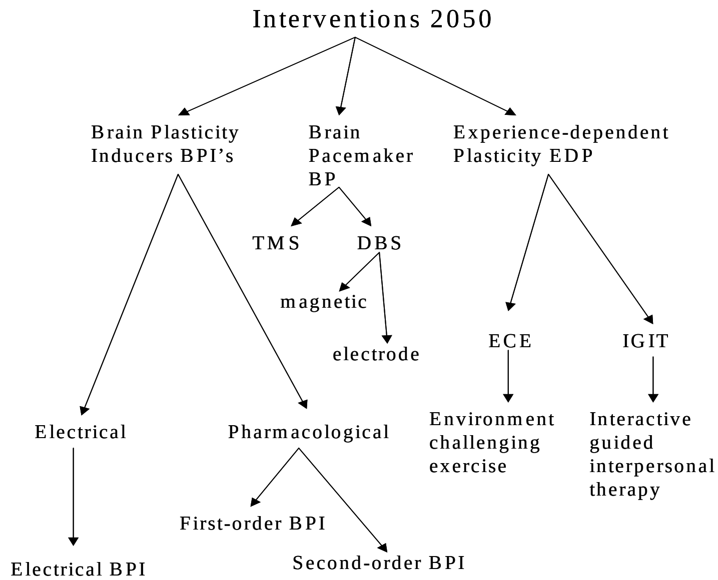
They became silent and Dan introduced himself and began his lecture. ‘There are three major Intervention modalities used in combination in every optimization process.’ He picked up a marker and turned to the board behind him, creating a flow chart as he spoke. ‘The first and most basic are the brain plasticity inducers—BPIs. There are two types of pharmacological agents—First-order BPI and Second-order BPI—and one electrical agent, which play a critical role in bringing the brain modifications needed for optimization of brain organizations.’

He glanced at the listeners then turned back to the board. ‘The second Intervention modality includes the brain pacing—BP, which involves external brain-locked interventions of electrical or magnetic currents in the millisecond range. The different BP modalities involve transcranial magnetic stimulation—TMS—and deep brain stimulation—DBS. The DBS can be magnetically induced as well as by transplanted electrodes.’

Another brief glance at the audience. ‘The third and last modality is experience-dependent plasticity—EDP.

This involves environmentally challenging exercise—ECE—and interactive guided interpersonal therapy—IGIT. The ECE uses virtual reality technology—VRT, which boosts presence, making it very effective. The IGIT is a newer, more suitable name given to what was once called psychotherapy. This name was given because the psychological change in psychotherapy was acknowledged to come about from interpersonal experiences, namely corrective experiences. It is termed guided because a professional therapist is involved and it is not merely a regular social interpersonal process. The new name was adopted because unlike psychotherapy, which was applied to relatively static brains, IGIT is applied to manageable brains during induction of plasticity with BPIs.' Dan paused and looked at the chart.

Figure 2: Intervention modalities



Dan pointed to the entry on the chart, 'Pharmacological BPIs became possible after findings from the first decade of this century revealed biochemical key factors for cellular interventions that increased and maintained neuronal plasticity. As early as 2004 it became evident that brain derived neurotrophic factor—BDNF—and cAMP response element-binding protein—CREB—up-regulators enabled powerful control over neuronal plasticity[1]. These factors have been found to enhance cell growth, synaptic sprouting and remodeling, neurite extension, long-term potentiation—LTP—and cellular resilience. This allows neurons to receive, process and respond to information and to adjust the signal generated by many different neurotransmitter and neuropeptide systems. It is these processes which give the state-space landscape organization of the brain[2] the flexibility and adaptability necessary to resolve many mental disorders emerging from disturbances of state-space dynamic organization of brain systems. Based on these early insights[3], the two medication categories were later established.'

Dan was feeling a little less uncomfortable now and began to slowly pace back and forth as he spoke. 'The first category is the First-order BPIs,' he said, pointing to the chart. 'It includes enzymes[4] and up-regulators[5]. The First-order BPIs are potent boosters of neuroplasticity that directly target the core molecules that actualize neuronal plasticity, the BDNF and CREB. These First-order BPIs have been found to be valuable in the first steps of Interventions to create phase transitions in the brain organizations.'

[1] Charney and Manji 2004
[2] Peled 2004
[3] Future 2022
[4] MAPK, PKA
[5] Bcl-2

A low murmur from the students and then all was quiet. Dan stopped his pacing and pointed to the chart again. ‘The second category is the Second-order BPIs. These include various combinations of inhibitors[1], potentiators[2], receptor antagonists[3], antagonists[4] and reuptake inhibitors[5]. The Second-order BPIs act on the more peripheral and regulatory agents. For example, the Glutamate inhibitors that counter-act the glutamatergic neurotransmission responsible for atrophy of CA3 pyramidal neurons[6]. AMPA potentiators and NMDA receptor antagonists are useful in enhancing MAPK, a molecular cascade that eventually increases CREB activity[7]. The first medications used to treat depression[8], before their BPI activity was appreciated, increase availability of the relevant neurotransmitters. This enhances mediated[9] activity that eventually increases CREB activity and BDNF formation. The Second-order BPIs are used after brain phase transitions are achieved, to maintain favorable conditions or augmenting additional phase alterations, as therapy requires.’

Dan pointed to the chart. ‘Electrical BPI,’ he said and resumed his pacing. ‘In the first years of this century, the behavioral and branching structural effects of combining subdural motor cortical electrical stimulation with motor skills training in adult male rats was assessed following unilateral sensory-motor cortex injuries[10].

Animals stimulated with 50Hz had a significant

[1] Glutamate
[2] AMPA
[3] NMDA
[4] Glucocorticoid
[5] Serotonin Norepinephrine
[6] McEwen 2001; Sapolsky 2000
[7] Skolnick et al. 2001
[8] Serotonin Norepinephrine reuptake inhibitors
[9] PKA G-protein
[10] Adkins and Jones 2003

improvement on the task after training and these results were coupled with increase in the surface density of branching processes in the cortex around the injury. The results supported the effectiveness of combining rehabilitative training with cortical electrical stimulation to improve functional outcome and cortical neuronal structural plasticity following sensory-motor cortical damage. Following work[1] perfected this technique of cortical electrical stimulation—CES. This was found to be significantly effective where documented brain tissue damage occurs, such as cerebral vascular accident, post operation brain tumor lesions and traumatic brain injuries. Electrodes are implanted over the cortical surface around the injury and electrical stimulation of 50Hz is delivered for a period of 10 to 15 days.'

Stopping in front of the chart, Dan said, 'Brain pacing.' He pointed to the relevant entry on the board. 'TMS involves placing a small coil of wire on the scalp through which a very brief and powerful current is passed. In rapid TMS, current pulses are repeated at a certain frequency. It was when the multiple-coil rapid transcranial magnetic stimulation—MCrTMS—was coupled to ongoing EEG and task-locked, as well as being mounted on a wearable helmet[2], that it reached its form known to us today as a brain pacer.'

Indicating the chart again, Dan continued. 'Being invasive, electrode-dependent DBS is avoided where possible. It is reserved for cases where massive phase transitions are required and could not be achieved with the regular BPI MCrTMS methods. In certain serious conditions, entire cortical activity may need massive excitations. This is only achievable by stimulations of brain-stem systems[3] that emerge from a particular area of

[1] Future 2029; Future 2031; Future 2039
[2] Future 2013-2015
[3] chatecholaminergic

the brain[1]. A better approach is to use TMS for DBS, which can be achieved with specially designed coils[2].'

Low murmurs rippled across the room. Dan waited until they stopped before moving on to the last treatment. 'It was natural that the ECE therapy followed the MRE VRSs. These scenarios were found to identify brain deficiencies, so it was logical to use them to repair these brain deficiencies. Based on this, the therapy plan became simple. For example, the VRS code of MI, TOM and PS that was used to identify brain insufficiencies in a specific individual would then be used to create that person's personal therapeutic exercise VRS. The individual would need to exercise those exact brain functions needing development. In the past, the idea of cognitive therapy along these ideas was ineffective because brain plasticity after a certain age was reduced to the extent that little change could be achieved in the brain. However, as it is done today, using BPIs, ECE has become extremely powerful, especially when improvement on subtle mental cognitive functions is targeted.'

Waving his hand at the chart Dan said, 'That brings us to IGIT.' He began pacing again as he spoke. 'Psychotherapy, the original interpersonal therapy, was therapeutically limited when detached from BPI. Later, it was recognized that psychotherapy had a neuroscientific foundation. Frequently, individuals seek psychotherapeutic treatment out of distress that originates from interpersonal relationships[3]. Psychodynamic therapy involves overcoming resistance, offering appropriate interpretations and increasing insight into relevant aspects of interpersonal relations[4]. According to the approach of plasticity in the

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[1] ventral tegmental area (VTA), reticular system locus ceruleus of raphe nuclei
[2] Zangen and colleagues 2004
[3] Explained in *Brain Dynamics and Mental Disorders*, Peled 2004
[4] Freud 1953; Michael 1986

brain[1], the psychotherapeutic process can be described as a physical change that takes place in the brain of the client.

Initially, the relations between the internal map of reference of the individual—the internal representations—and some aspects of the psychosocial situations the individual encounters, do not match. This incompatibility reaches the extent where perception and reaction to those psychosocial situations are distorted and interfere with the psychosocial functioning of the individual. The psychosocial dysfunction is generally accompanied by distress, which is typically expressed by symptoms of anxiety and depression. By gradually changing the global formation to a favorable configuration, the therapy enables the incorporation of an interpretation and the therapist overcomes the resistance to that interpretation. Repeating this process over and over again will eventually reshape the state-space of the brain to increase the complexity of internal representations and the psychological repertoire of the individual. These changes transpire and are maintained by the experience-dependent plasticity processes of the brain. With the application of BPIs the brain can actually assume the plasticity levels of the infant or child brain, allowing for an extremely more effective psychotherapy meriting the new name of IGIT.'

Dan stopped and faced the students. 'That sums up the different modality treatments available to optimizers in their treatment of patients. I suggest you read up on the history of these treatments, I'm sure you will find it interesting.' The students filed out of the room, discussing the lecture amongst themselves. Dan followed the last one out and went straight to the staff lounge for a much-needed cup of strong coffee.

[1] Peled 2004

Chapter 37

Nearing the open door of the staff lounge, Dan could hear Professor Krauss speaking inside.

'Until the second and third decades of this century,' said the professor, 'the ability of psychiatrists to treat mental disorders was very limited. This was because of two reasons. First, knowledge about what goes wrong was not available and second, the ability to manipulate and change brain organization was limited.'

Dan entered the room and saw that the professor was speaking to Helen. He went over to make himself a drink while Professor Krauss continued. 'In the 2000s it became common to indicate organization changes in the brain with the term plasticity. This term actually had its roots earlier and was applied to stimulus-dependent brain organizations by terms such as experience-dependent plasticity.'

'The more effective drug treatments[1] are from the 80s of the previous century, aren't they?' asked Helen.

'Yes,' replied the professor. 'They turned out to be relatively powerful plasticity inducers, although their plasticity inducing effects were not appreciated at all until the beginning of this century. Today, large arsenals of Intervention modalities are available for psychiatrists in their treatment of mental disorders. These are used in repetitive therapeutic processes directed toward optimizing brain organization.'

'I'd like to hear more,' said Helen 'But I am due on the ward.' She turned to Dan, 'Will we see you there today, Doctor?'

'Er, yes,' said Dan.

[1] SSRIs, serotonin-specific reuptake inhibitors

Helen nodded and he watched her walk out the door. Dan turned back to the professor and saw he was smiling. Dan flicked a hand through his hair and sat down.

'Do you have a problem?' asked Professor Krauss, looking concerned.

'No,' replied Dan. 'I gave my first student lecture this morning, on the different optimization treatments.'

The professor chuckled. 'I'm sure you did well.' He leaned back and laced his fingers across his middle. 'Treatment modalities,' he said, looking up at the ceiling. The professor smiled, his eyes settling back on Dan. 'Initially, TMS first made its way as a popular research topic, and later became part of the optimization process. TMS was introduced[1] as a technique that uses the principle of inductance to get electrical energy across the scalp and skull in order to produce changes in neural activity in the brain.'

'Producing a magnetic field that passes unimpeded through the tissues of the head,' responded Dan.

The professor nodded. 'The magnetic field, in turn, induces a much weaker electrical current in the brain that is capable of activating nerve cells in the cerebral cortex. Although small, these electrical currents have been shown to influence—typically disrupting but sometimes enhancing—cortical neuronal activity in speech[2], memory[3], and motor control[4].'

Dan sipped his drink as Professor Krauss spoke. 'TMS was used as a tool to study and alter brain dynamics,' continued the professor. 'Repetitive transcranial magnetic stimulation—rTMS—was found to modulate cortico-cortical connectivity[5].' He paused then went on, 'It was

[1] Barker et al. 1985
[2] Pascual-Leon et al. 1991
[3] Pascual-Leon and Hallett 1994; Grafman et al. 1994
[4] Pascual-Leon et al. 1994
[5] Keck 2003

shown[1] that regional cerebral blood flow—rCBF—response was enhanced or reduced after application of a fast rate or slow rate rTMS, respectively. This suggested that the changes in rCBF induced by rTMS reflect lasting modifications in stimulated synaptic effectiveness. Moreover, it was shown that reduction of rCBF, using rTMS stimulation, in normal patients, significantly impaired performance in a cognitive task[2]. This historic work suggested that TMS could be used to alter brain activation dynamics and possibly even alter cognitive performance.'

Dan put down his cup. 'Applications of TMS to mental disorders began at the same time as studies of TMS on the normal brain,' he stated. 'Initially, it was thought to use TMS to replace electroconvulsive therapy—ECT—for depression. There was no neurophysiological reason for it, other than that of electrical current being induced.'

'Later on,' said Professor Krauss, 'purpose-guided experiments began. It was shown that low-frequency TMS, less than 1Hz, to temporo-parietal cortical regions can reduce auditory hallucinations in what was then called non-responsive hallucinating schizophrenic patients[3].'

Dan nodded. 'At about that time, it was also shown[4] that rTMS could enhance human cognitive performance when applied to individual EEG alpha frequency.'

'Correct,' nodded the professor. 'Based on the findings of task-related task performance EEG alpha desynchronization, individual alpha-related rTMS was applied to two areas of the cortex[5], suppressing upper alpha

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[1] Keck 2003
[2] Keck 2003
[3] Hoffman et al. 1999
[4] Klimesch et al. 2003
[5] mesial frontal (Fz) and right parietal (P6)

power during task presentation and in doing so, achieving enhanced task performance[1].'

Dan looked directly at the professor. 'It was just a matter of time before research groups[2] learned to control EEG frequencies with rTMS.'

'Yes,' said Professor Krauss. 'Their work continued upgrading rTMS to form multiple coils apparatuses, the MCrTMS. By then, these systems could achieve control over brain synchronizations in multiple regions[3], which could directly control brain transcortical connectivity.'

Dan thought for a moment. 'Compared to the earlier trial-and-error discoveries, the MCrTMS reflects a more skilled, theory-oriented approach to finding effective treatments for mental disorders.'

The professor sat forward, looking intent. 'One can imagine that combining BPIs with MCrTMS can have a powerful effect on alterations of brain organizations.' He stared at Dan. 'This kind of Intervention requires careful assessment of brain complexity organizations and carefully designed timed and synchronized algorithms of Intervention.' Dan nodded. 'These Interventions are powerful, especially to induce increasing levels of neural complexity where and when it is needed. This system pushes the brain back to desired forms and levels of organizations, achieving phase transitions.' He sat back.

Dan shook his head. 'I don't know how we could cure mental disorders without the tools available to us now.' He looked at his watch and remembered he had an appointment. 'I have to go to the ward and speak with Steve's mother, to discuss his condition and treatment,' said Dan as he stood.

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[1] Klimesch et al. 2003

[2] Moses et al. future 2006; Levite Binun et al. future 2006; Future 2010; Future 2012

[3] Future 2019; Future 2022

‘Ah,’ responded the professor. He looked purposefully at Dan’s hair and frowned slightly.

Dan grinned and smoothed his hair down as he headed off to the ward.

Chapter 38

When he arrived at the nurses' station, Dan was told that Steve's mother was waiting for him in consultation room one. He entered the room and Iris looked at him with a mixture of dread and hope in her eyes.

'Hello Dr Moor,' she said. 'Can you help my son?'

'Yes Iris,' replied Dan and proceeded to explain Steve's condition and the treatment he would receive. When he left her, Iris was a much happier person.

Back at the nurses' station, Helen greeted him. 'Pamela's mother would like to speak with you when she comes in, if you have time. She will be here shortly.'

'All right, I'll wait here for her,' replied Dan.

Helen began sorting empty sample bottles into containers. 'I see that Tim's treatment requires only BPIs and ECE.'

'Yes,' said Dan. 'The two together are extremely effective.'

Helen stopped what she was doing and looked at Dan. 'Tell me more about ECE. VRS is my weak spot, remember?'

'Right,' smiled Dan. 'Past experiences with cognitive training was not neglected, it was integrated within the newly developed VRSs. Some of these training schemes came about as developments of older methods, such as problem solving exercise—PSE—goal management training—GMT—and TOM. PSE used analysis of complex problems, breaking them into manageable components, forming viable alternative solutions and choosing among these solutions.'

'I'm listening,' said Helen as she started working again.

'This was done by increasing awareness of deficits and goal-directed ideas. GMT was achieved through training in discrete stages of goal completion, including assessing a situation and directing attention toward relevant goals, selecting appropriate goals and partitioning these into subgoals, encoding and retaining these goals and subgoals, and monitoring the outcome of an action in regard to the desired goal[1].'

Dan absently passed empty containers to Helen as she filled and stacked them. 'Past experience using TOM involved working with schizophrenia patients at the start of the century. Thirty severely delusional patients, completely lacking insight when interviewed about their delusions, were investigated[2]. At that time, it was claimed that the patients suffered impaired meta-representation, later known as TOM. Moreover, it was claimed that the presence of delusions was correlated to poor TOM performances. TOM techniques were used where perspective was shifted from the first person to third person.' Helen stopped what she was doing and looked at him. 'This work was one of the first to suggest that in some delusional patients, it may be possible to gain access to and modify their mental states using TOM training. Subsequently, when presence with VRT was developed, this TOM training received a boost of power regarding its cognitive influences. With VRT it was possible to alter the patient's convictions as to false ideations either by attributing the patient's experience to a third person[3], or by contrasting the belief by the virtual environment.'

Helen thought for a moment. 'Like a warm welcoming invitation to join the agency for a patient convinced that the agency is after him to kill him?'

'Yes,' Dan nodded. 'It was only after the ECE was coupled with BPI that it became therapeutically effective.'

Helen was about to respond when Pamela's mother appeared at the desk. 'Hello Margaret, Dr Moor has been

[1] Levine et al. 2000
[2] Gambini and colleagues 2004
[3] Gambini

waiting for you,' said Helen. She turned to Dan, 'Consultation Room 1 is available, Doctor.'

'Thank you,' said Dan. 'This way, please Margaret.' He looked back and saw Helen smiling.

Chapter 39

Once they were seated, Dan explained Pamela's treatment. 'Pamela will receive medication and interactive guided personal therapy.' Margaret nodded once. 'Initially, the relations with the therapist repeat the same patterns of interpersonal relations that caused the distress. The therapist identifies the malfunctioning interpersonal patterns and acts, during therapy, in a way that gradually changes the attitudes of the client to similar situations in the future. This therapeutic Intervention is termed correcting experience. Better coping in psychosocial situations reduces suffering and enables the relief from symptoms.'

Margaret said nothing.

Dan continued, 'The goal of the therapy is to reshape the internal representations to include the appropriate internal configurations to cope with the psychosocial situations at hand. Initially, the client perceives the therapist as a person from their past. We call this transference. This is because the client activates the attractor systems of their brain which represent the person from the past. Since the therapist is not the same as the activated representation, a distorted perception of the therapist emerges. Due to this distortion, an inappropriate behavioral reaction to the therapist occurs. Most likely, this distortion occurs with other interpersonal situations outside the therapeutic sessions. This indicates that there is substantial mismatch between the internal representation and the psychosocial reality.'

'Wait,' said Margaret, frowning deeply. 'Are you saying that Pamela has set ways of receiving and processing information and can't accept things that are different?'

Dan inclined his head. 'Basically, yes,' he said. 'The therapist acts to enlarge the repertoire of representations of the individual to match many more different psychosocial situations. In other words, the psychotherapeutic process increases the neural complexity in the brain of the client. When the therapist reacts to the client in new ways that were never perceived before, Hebbian mechanisms of plasticity will gradually create the new attractor systems needed for the additional internal representations. In this manner, the therapist shapes the space-state topology of the brain to form new internal representations. This process probably creates actual changes in the functional connectivity of the neural systems involved, making it a physical process in the brain.'

Margaret was staring intently at Dan. He could see she wanted to say something so he waited for her to speak. 'So,' she began slowly, 'the therapist will help Pamela's brain to be able to accept things that are different or new.'

'You could put it that way,' said Dan. 'The process is actually much more complex than the description I gave. For example, due to a lack of representational systems, the interpretations offered by the therapist are often denied and do not gain access to the global formations. These interpretations will never reach conscious levels—what we call resistance, in psychoanalytic terminology. The information simply does not satisfy the constraints of the global configuration. Instead, it conflicts with the message in the global workspace.' Margaret frowned but said nothing. 'For an interpretation to succeed, it must be delivered at the right time, when the individual is ready for it[1]. There must be a certain constellation of the global organization, which is favorable for including the new patterns of information proposed by the interpretation. The therapist first prepares the patient by repeated clarifications, confrontations and other interpretations. This process changes the global formation, moving it slightly toward the pattern that will be favorable for accepting the critical

[1] Michael 1986

interpretation, the one that will induce the change. The importance of overcoming resistance in psychotherapy was documented long ago[1].'

Margaret thought for a few moments. 'This could take a while, then,' she stated.

Dan nodded. 'It is probably the increase in neural complexity that improves psychosocial adaptability. In turn, psychosocial adaptability reduces the suffering that originates from conflicts of interpersonal relations. In other words, the outcome of psychotherapy is relief of distress in interpersonal situations. It is achieved via the reduction of specific sensitivities of personality traits and the increase of flexibility and adaptability to changing psychosocial situations.'

'We have a long road ahead of us,' said Margaret. She smiled. 'Thank you for looking after my Pamela, Doctor.'

'No problem,' said Dan. 'Pamela is a good patient.' They got up and he held the door for her as she left.

[1] Freud 1953

Chapter 40

It was a week later that Dan entered the cafeteria very early, expecting to be the only customer. He was surprised to see Professor Krauss seated at one of the tables, reading a paper. Dan went to the counter and loaded a tray with a hearty breakfast, then made his way to the professor's table.

Professor Krauss looked up and smiled warmly. 'Dan. Good morning. You are exceptionally early today.'

Dan sat down and looked at the professor. 'I am to present reports on my patients to Dr O'Connor today at the weekly ward meeting.' He ran his hand through his already tousled hair.

'Ah,' nodded the professor, glancing at Dan's tray. 'I see you are fortifying yourself for the task. Enjoy your breakfast and I look forward to hearing your report at the meeting.'

'Thank you,' said Dan and set to work on his breakfast. The professor got up and ambled out of the cafeteria.

The door of the meeting room was closed when Dan arrived. He smoothed his hair and pushed the door open. Dr O'Connor, Professor Krauss and a number of other doctors were already seated around the large table.

'Dr Moor,' said Dr O'Connor. 'We will hear your report first.'

Dan handed copies of the Validation results to Dr O'Connor then detailed the Investigation and Validation phases of his three patients. The other doctors listened with interest but it is the therapy advancements of the Intervention phase that peaks the attention of all optimizers in these meetings. The knowledge and tools provided through ongoing research heightens the interest in the Intervention phase.

Dan presented Steve's treatment first. 'After I received preliminary results of the SCE_{system} I put Steve on First-order BPI boost. This was necessary as both clinical as well as SCE_{system} results indicated fragmentation of global workspace dynamic core organizations. This was validated by the MRE.' Dan looked at Dr O'Connor, who showed no reaction. 'Currently, he is on First-order BPI boost as well as EEG coupled MCrTMS. I have started a two-week MCrTMS Intervention after allowing a first week of only First-order BPI. Additionally, I have started an ECE involving a hundred percent MI-VRS. Preliminary EEG analysis showed a decoupling of frontal-to-parietal cortices, which was severe at the start of the Intervention. This has already reduced and I predict that in the second week of Intervention Steve will have re-coupled these systems and may go on to finer-tuned global workspace integration, allowing for organization of an integrated dynamic core. It is pleasing that, clinically, he is already cured of most of his segmented dynamic core symptoms—or positive symptoms, as they were once called.'

Dr O'Connor's look became more piercing. 'In your Intervention plan for Steve, did you consider your findings of hierarchical deficiencies?' Before Dan could reply, Dr O'Connor continued. 'As you know, in order to get an optimal high-level dynamic core in terms of complexity, the entire brain system will need to undergo a phase transition to recreate and bring back the higher-level transmodal control over the hierarchy.'

'Yes. I have considered that,' Dan responded. 'And my next step after a recurring MRE test is to apply a DBS together with a TOM code added to the ECE Intervention.'

A brief moment passed while Dr O'Connor looked over the MRE results. 'In Steve's case, it may have been possible to start with the DBS procedure.' He looked at Dan. 'The dynamic core global integration and the hierarchical reconstruction could have been simultaneously achieved. Please schedule Steve's MRE control for tomorrow and bring the results to me. We will decide how to proceed in his case together.'

Dan nodded and made a note to reschedule Steve's MRE as soon as he left the meeting.

Dr O'Connor looked at Dan's sheets. 'Your next patient?' he asked.

'Tim,' Dan answered. 'Tim had a frontal lobe transplant and was immediately started on First-order BPI boost as well as ongoing electrical BPI.' Dr O'Connor nodded. 'I will start him on ECE coded MI = 0.33 TOM = 0.33 PS = 0.33.'

'Hmmm,' said Dr O'Connor. 'Wait another week before you start the ECE. Dr Moor, do you know why it is best to wait another week in this case?'

'Yes,' Dan responded quickly. 'With the BPI just starting, the neuronal networks might still be relatively static, which would form ECE-dependent fixed circuits. This would happen due to formation of overly static Hebbian connections and then the entire global organization might develop local minima that will trap the system, reducing its dynamics as well as its neuronal complexity.'

'That is correct,' said Dr O'Connor.

Dan added, 'If that did happen, it is possible to correct it by additional DBS-rTMS later.'

'There is no reason to add a relatively invasive DBS Intervention if you can avoid it,' said Dr O'Connor.

Dan added a note to schedule Tim's ECE for one week's time. He looked at Dr O'Connor and continued his report. 'My final patient is Pamela,' said Dan. 'In Pamela's case we first needed to increase plasticity to reduce deoptimization dynamics, just as the old antidepressant medication did. I have put her on second-order BPI and ordered IGIT.'

‘Good,’ approved Dr O’Connor. ‘You can delay IGIT for one month only. By then you should have MRE confirmation that attractor systems are no longer deoptimized. There are new findings that indicate much better results in P-coded state-space developments—such as immature personality—when First-order BPI is used. You might consider First-order BPI for the first 6 months of IGIT.’

Dan made a note to look up this new information, and then focused on the next doctor’s presentation.

Chapter 41

Dan was at the nurses' station checking his patients' progress when Iris arrived with a big cake for the staff. She was smiling broadly as she turned to Dan.

'Thank you Dr Moor. You are giving my son back to me again. It has been so long since he was himself. Now he is becoming more like he was before.'

Dan returned her smile and knew that the first level of dynamic core integration is obvious, from clinical perspectives, because many easily-observable symptoms go away. However, the more subtle symptoms of hierarchical insufficiency—termed negative signs in the past—still needed to be treated and the DBS phase of Steve's Intervention was still ahead.

'I am glad you see that improvement,' he answered. 'We will continue treating him and, as I explained to you, there is still an important Intervention to come.'

Iris, still beaming, nodded. 'I remember. I know you will make my son completely well again. Thank you Doctor.'

Dan gave her an encouraging smile and went off to do his rounds.

Steve was sitting up in bed when Dan entered his room. 'Hello Steve,' said Dan. 'How are you feeling today?'

'All right. A bit tired,' answered Steve.

'That is to be expected. I prescribe a good night's sleep,' said Dan with a smile.

Steve smiled in return and Dan left, pleased with Steve's progress.

The door to Tim's room opened, just as Dan reached it. He stepped back to allow the nurse to pass and noticed that the light was off in Tim's room. He saw that Tim was sleeping and raised his eyebrows in silent question.

‘His family was visiting,’ said the nurse, ‘and it seems to tire Tim.’ She pushed the door fully open and secured it.

‘Ah,’ said Dan. ‘I’m glad to hear his family is coming to see him. The support is good for Tim and the visits are also good for the family, it means they are over the initial shock of Tim’s accident and injury.’

‘Yes,’ said the nurse. ‘I suppose they thought that Tim would remain the way he was when he arrived here.’

Dan nodded and continued down the corridor.

Pamela appeared pleased to see Dan when he arrived. She was looking a little less pale and the darkness under her eyes had disappeared.

‘How are you today?’ asked Dan.

‘Not bad,’ replied Pamela. ‘I’ve started reading a book that’s quite good.’

‘That will make the time pass quickly,’ commented Dan. ‘But no reading after lights-out,’ he added with a mock frown that changed to a grin.

‘No Doctor,’ said Pamela, with a small smile.

Returning to his office, Dan found paperwork waiting for him on his desk. There was an insurance questionnaire about Tim’s medical condition that was marked urgent. Tim’s insurance company wanted a prediction about improvement and possible handicap. Feeling someone’s presence, Dan looked up to see Helen standing in the doorway.

She shook her head. ‘No matter how much technology advances, with accidents there is always paperwork for insurance companies and lawyers,’ she said.

‘I can’t imagine how psychiatrists in the past coped with these legal opinions or even forensic liabilities,’ Dan said, ‘with no valid reliable clinical tools for assessment, or even a reliable diagnostic system.’ He thought for a moment and then said, ‘I must ask Professor Krauss if this was one more reason why psychiatry was not highly valued among the medical sciences in the past.'

'Hmmm, could be,' commented Helen, going into the kitchen area.

Dan filled in the information about Tim. In the Predicted Improvement section required by the insurance company, Dan added the MRE predictions for Tim's recovery. 'It is that simple now,' he said. 'The MRE has the simulation capacity to use comparisons between optimal brain functions and the current deficient ones and together with follow-up of brain organization parameters, the algorithms accurately predict results and timing. This could not have been possible in the era before the MRE.'

'No,' agreed Helen.

Dan finished filling out the legal papers for Tim and glanced over the daily report.

Helen re-appeared in the doorway. 'It was good to see that Pamela's mood improved today.'

'Yes. The Second-order BPIs are working,' said Dan, packing his briefcase. 'Are you ready to leave?'

Helen nodded and as they left, he reminded himself to read the papers about using First-order BPI with IGIT for P-level state-space organizations.

Chapter 42

It was three weeks later that Dan was going over his notes while he had breakfast in the cafeteria, preparing to present his patients again at the weekly meeting. After a hearty meal, he went to the meeting room.

He was not the first speaker today and listened with interest to the other doctors' presentations. When it was his turn, Dan projected a summary table onto the wall to show the Intervention modalities used in the treatment of his patients.

Table 1. Optimization Intervention schedules

Steve	Tim	Pamela
SCEsystem results	Frontal-lobe transplant + first-order BPI boost + electrical BPI	Second-order BPI
'First-order BPI' boost		IGIT
MRE	ECE MI 0.33, TOM 0.33, PS 0.33.	First-order BPI
MCrTMS		
ECE MI = 1.00	Second-order BPI + ECE MI 0.33, TOM 0.33, PS 0.33.	IGIT
MRE control		
DBS + ECE MI 0.5, TOM 0.5.		
MRE control		
BPI second order + ECE MI 0.5, TOM 0.5,		
MRE control		
BPI second order, monthly ECE MI 0.5, TOM 0.5, for one year		

‘As you can see by Steve’s schedule,’ said Dan, ‘his MRE had shown insufficient hierarchical levels with improved global-workspace organization, so the DBS intervention had to be applied earlier than I first planned.’

‘Global organizations would not last long if hierarchical organization is not accomplished first,’ explained Dr O'Connor. ‘Hierarchical organization can be achieved at the same time as integration of dynamic core activity and this was desired in Steve’s case.’

‘Following that,’ continued Dan, ‘phase-transition with balanced hierarchical stable transmodal systems was achieved for Steve’s brain. He was switched to BPI Second-order and an ECE coded MI:0.5, TOM:0.5.’ He looked at Dr O’Connor who nodded slightly. ‘Steve is practically symptom-free and can be discharged with an ongoing Intervention of one year of stabilizing BPI Second-order and a monthly ECE of the same code.’ There were murmurings of approval around the table. ‘Steve has passed the examinations to be accepted back into law school, which shows that he is gaining his former capacities and motivations,’ Dan concluded.

Comments were exchanged and then Dan moved on to his next patient. ‘Tim is progressing very well with the optimization process,’ he said. ‘After three weeks of First-order BPI boost and electrical BPI with ECE coded MI:0.33, TOM:0.33, and PS:0.33, he has been switched to Second-order BPI while continuing the same ECE coded format. In three weeks time he will have a final MRE control and should be able to conclude the Intervention phase.’ There were murmurs and nods from the others.

Dan completed his presentation. ‘Pamela has resumed a stable mood and the MRE control from the last day showed no deoptimization dynamics. She has started the IGIT part of her Intervention phase and has been switched to First-order BPI to boost initial IGIT effect.’

Dan returned to his seat and discussion broke out around him. He looked towards Dr O'Connor who nodded and almost smiled. 'Well done,' said Professor Krauss from across the table, his eyes twinkling brightly.

Chapter 43

One year and many patients later, Dan arrived at a forensic psychiatry meeting on the subject of patient's legal rights during their illness. Dan entered the room and looked around for an empty seat. He noticed someone on the far side waving to him and made his way in that direction.

'Have a seat Dr Moor,' said Clare, patting the chair beside her.

'Thank you,' replied Dan.

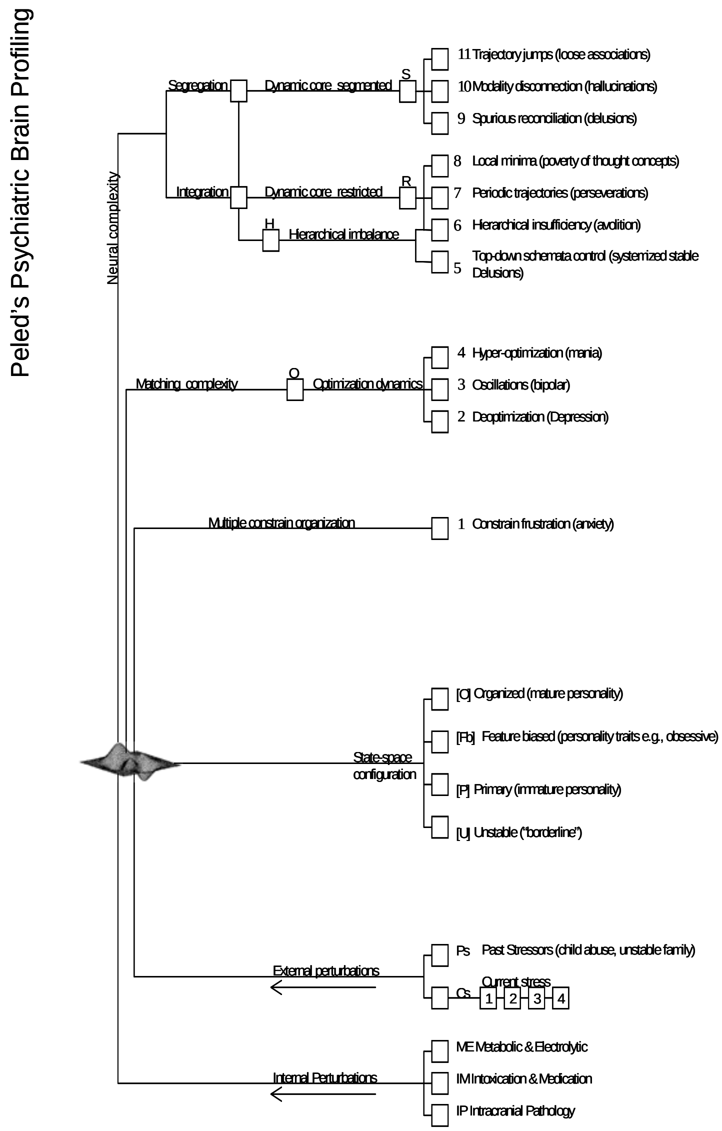
'Sonny and Todd will be here shortly,' said Rachel, indicating two more empty seats beside her.

The two young men arrived just as proceedings began. A young, well-groomed lawyer approached the lecture stand to advocate for patients' right to optimization Interventions at first hospitalization, and the right for everyone to have access to that procedure.

Dan smiled as he recognized the young lawyer. 'Steve,' said Dan to himself. 'No wonder he is in favor of optimization. He is a product of it, an example of its effectiveness.' He sat forward, 'Now I will learn from him.' And he concentrated on Steve's passionate lecture.

Appendix
Chart 1.

IP, IM, ME, Cs 1 2 3 4, Ps, – [U, P, Fb, O] – 1, ***O*** 2 3 4, ***H*** 5 6, ***R*** 7 8, ***S*** 9 10 11.



Abbreviations

ACC anterior cingulate cortex
BDNF brain derived neurotrophic factor
BPI brain plasticity inducer
BSAO brain-system analysis output
BWS bedside wellness system
CES cortical electrical stimulation
C_M matching complexity
C_N neural complexity
CREB cAMP response element-binding protein
Cs current stressors
DBS deep brain stimulation
DG data glove
DLPFC dorso-lateral prefrontal cortex
ECE environmentally challenging exercise
ECT electroconvulsive therapy
EDP experience-dependent plasticity
EEG electroencephalography
EI exploration intervention
ERP evoked response potential
ES embryonic stem
fMRI functional magnetic resonance imaging
FPC frontopolar cortex
GMT goal management training
HMD head mounted display
HR haptic rendering
IAIM image analysis input matrix
ICA independent component analysis
ICU intensive care unit
IGIT interactive guided interpersonal therapy
IP intracranial pathology
LORETA low-resolution electromagnetic tomography
LTP long-term potentiation
MCrTMS multiple-coil rapid transcranial magnetic stimulation
MEG magnetoencephalography
mES mouse embryonic stem
MI multimodal integration
MRE multimodal reconstructive encephalography
MRI magnetic resonance imaging
MTL medial temporal lobe
NSC neural stem cell
P primary state-space configuration

PBP	psychiatric brain profiling
PET	positron emission tomography
PFC	prefrontal cortex
Ps	past stressors
PS	psycho-social
PSE	problem solving exercise
REM	rapid eye movement
rCBF	regional cerebral blood flow
rTMS	repetitive transcranial magnetic stimulation
SCE_{system}	speech cognition estimator system
SDC	stored data comparison
SPECT	single photon emission computed tomography
TBI	traumatic brain injury
TMS	transcranial magnetic stimulation
TOM	theory of mind
VR	virtual reality
VRS	virtual reality scenario
VRT	virtual reality technology

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