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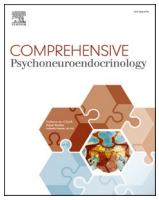

Oxytocin and our place in the universe

Julie R. Korenberg

Pediatrics and Neurology, University of Utah, United States

A R T I C L E I N F O

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A B S T R A C T

Is the oxytocin-vasopressin (OT-AVP) system a part of the unseen force that subtly (in a clever and indirect way) directs our human fascination to ourselves? And is it possible that this fundamental drive is the inevitable handmaiden of the genetic selection for survival and reproduction that is played out at the level of the individual, the family and the society? Perhaps. But an equally intense biological drive to experience the unknown is intertwined and exists in the individual as "curiosity". Both are essential for survival and success of the species. Curiously, the path to understanding ourselves, the joy of discovery and joining with others on this imperial journey to the OT-AVP system may itself be driven by the same system. I have been driven and inspired to understand "Us" for some unseen reason. This chapter relates how a driving curiosity and search for meaning led to the critical training and inspired mentorship essential for developing novel genetic, cellular and imaging technologies necessary for each advance toward this deeper understanding. Specifically, the chapter describes my recognition of human "Genetics" as the hub of medicine and the language of human neurobiology. We then set out the rationale for and sequential development of four technologies (dense whole genome arrays of genomic markers integrated with the recombination map; needed to genetically dissect and define the genetic contributions to the distinct features of brain and social behavior in Down syndrome and Williams syndrome. These include generation of 1) dense whole genome arrays of genomic markers integrated with the recombination and gene maps for defining rare cases of WS differing by one or more deleted genes, 2) analytic methods for parsing genetic contributions to standardized outcomes of cognitive and behavioral data, 3) technologies using multicolor and multi temporal fluorescence *in situ* hybridization to define the subcellular and neuroanatomic localization of candidate genes in the non-human primate (macaque) brain, and 4) an approach to integrating timed measures of blood neuropeptides and genomic DNA sequence variants with self-reported religious experience in devout members of the LDS church. Working across evolution and ontogeny at the cellular, neural systems and organismal levels, has led to a suspicion that a bit of the grand design may involve OT, AVP and their partners in the subtle and artful processes of the last one-half billion years that link survival of our species with our prized capacity for abstract thought and spirituality.

1. God, space and the unknowable

From age six years forward, I was obsessed with the question of where space ended. I was also deeply concerned about the existence of God, sought sources of evidence for the paranormal, and considered the more immediate question of what I might be willing to sacrifice to have answers to these. The central metaphysical question seen through the eyes of a child was whether I would, if invited by aliens who landed in my garden patch, go willingly to their civilization, with no certainty of return, possibly to be dissected or exhibited in a zoo. The answer was yes.

Privately, I was consumed by ultimate questions of our being on earth, was in awe of the universe, and had an intense curiosity with respect to the limits of human experience. After a summer school classmate brought in a human larynx in a jar, and the wonder of human sound production was revealed to be related to the passage of air combined with muscle-controlled vibration of the vocal cords, I began to think that other ultimate and existential questions might be answerable with the tools of science. This illuminated my imagination and has never loosened its grasp nor its exhilaration. This drive to understand the meaning of human existence in the universe and God was combined with an inexplicable urge to stop and help care for the injured as the family car passed accidents.

The path forward led me to complete a PhD in genetics and postdoctoral fellowships in evolution and embryology and eventually to train in medicine. What began as intense curiosity, a fascination with

E-mail address: Julie.Korenberg@hsc.utah.edu.

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"how?" and "why?" and awe at the answers, very early combined with imagining different solutions to problems as an internal "virtual" prelude to narrowing and forging practical solutions. I made a conscious decision to acquire the skills, training, and counsel of the wise that were necessary to explore and answer the vast array of questions that fascinated me in childhood: humans, human welfare, and our place in the universe. I increasingly focused my research on humans as the critical model, using others (flies, rodents, primates, cells) as necessary to patiently determine the crucial missing information required to discover a role for specific genetic substrates, neural circuitry, and specific molecules, including oxytocin, vasopressin and their receptors, that enabled our interface with each other and our universe. I learned to use emerging science tools and developed others as needed to integrate genetics and cellular biology, and then to image structure and function across 10^8 levels, ultimately using electron and fluorescence microscopy through human neural imaging. The ultimate goal was to examine the nature of humanity and its evolution from genomes to brain and spirituality. My professional journey has lasted over half a century and, to this day, continues to engender the incomparable feeling of impending discoveries that may change our world for the better.

2. Genetics as the language of biology and medicine

It was the shared unique humor, brilliance, and human insight of mentors such as Professor John Southin, whose course in Molecular Genetics at McGill University, revealed the world of Genetics as the *lingua franca* of biology and medicine whether in flies (*Drosophila melanogaster*) or humans (*Homo sapiens*). For training please see summary below. This was a critical first experience as an adult, not being alone with wonder and a clear realization that the most profound human properties might be amenable to genetic dissection. The fundamental insight was that genetic dissection of biological processes required well-defined, measurable phenotypes for fly eye color or human behavior. It became clear to me as an undergraduate majoring in psychology, genetics, and divinity that to solve any problem of human behavior or disease, it was necessary to acquire the depth of knowledge and judgment that came only by sitting at the feet of the masters of one's field and understanding the limits of current knowledge. Although I felt that the questions of human existence lay at the intersection of multiple fields, notably behavioral and cognitive psychology, a semester at the University of Wisconsin Department of Psychology suggested that, although the field was developing rigorous methodologies and insights, behavioral-cognitive-brain phenotypes were not yet sufficiently defined at the individual level and human genetic models were even less so. There was work to be done.

3. Understanding humans lies at the intersection of genetics, brain and behavior: graduate school in basic science

The course of my life was changed by acceptance to graduate school in genetics at the University of Wisconsin, Madison. There, in the 1970s, I was surrounded by brilliant, self-effacing fellow graduate students and began the welcome journey of rugged, monastical self-discipline necessary to experience the shared joy of discovery. There, I found uncompromising integrity, a ready acceptance of ambiguity, and a fearless dedication to understanding the unknown. I was quite alone among my friends in my focus on forging human models as experimental organisms. But I was surrounded by an unrivaled richness of knowledge and blessed by an incomparable support for my vision.

Science, like religion, was a way of life. I began to feel at home in science through interacting with fellow students, postdoctoral fellows, and professors who were equally curious and passionate about unraveling the mysteries of the cell, development and evolution and, at the same time, who loved music and art. Three further shared qualities set the tone for my next decades as a scientist; humility, integrity and courage to report work that contravened accepted paradigms. This lesson would be needed in applying genetic approaches established in flies and corn to analyze gene contributions to physical brain features and behavior in humans. Nonetheless, this was a "golden age" (1950–1980) in cross-disciplinary discovery that began to reveal how many cellular processes existed in common across vast evolutionary timescales, including plants and animals.

4. Understanding human behavior requires developing the genetic and behavioral tools for parsing the human genome and human behavior: first, know your organism

The cellular mechanisms that are common across evolution for DNA, RNA and proteins suggested to me that these cellular processes could ultimately be parsed in human cells and related to an individual's brain structures or behaviors. The major challenge was how to begin to apply these insights in humans. My fascination with humans was unique in a graduate department studying bacteria, flies, corn, lilies, and, recently, human cells. All of this was occurring at a time prior to the development of DNA sequencing and cloning. However, based on those systems, it became clear to me that understanding the genetics of human behavior required new tools for elucidating the human genome and for parsing the features of human cognition, emotion, and brain. Therefore, in 1976, I moved from my genetics and basic sciences training to a unique program at the University of Miami. There I joined 27 others who also held doctorates in the sciences or engineering and wished to solve human problems. I spent the next 23 months in an intense medical school program, learning the inner workings, physiology, neurology, and disease states of my experimental organism. Medical training provided a foundation for the next step which would be applying basic genetic concepts to humans.

The human genome project was moving quickly, although it was (and remains today) only rarely focused on specific human behaviors. Hundreds of other scientists were elucidating the neuroscience of behavior across a wide array of organisms and systems. The magnitude of the "bottom-up" information needed to apply this bewildering array to humans was a virtual impossibility in that there were no hints regarding which gene system might be applicable. In contrast, I reasoned that a "top-down" approach that began with a human syndrome associated with spirituality or social behavior would provide an answer related to humans. My goal became to pick a specific condition, generate the genomic tools to find the genes involved, and then narrow down genes using rare cases and finally prioritize these biological or *in vitro* evidence of "causation". There is no question that the magnitude of the former task was inaccessible to a geneticist. However, the same drives that forced me to try to understand the universe and to help people in need pushed me forward.

After several decades, my two paths would eventually converge in studies of the human brain and behavior. As detailed below and in earlier papers, my goal would be to use genetic variation and anomalies to elucidate the role of the human genome and specific chemical pathways in human brain and behavior. On this long journey, like others in this Special Issue, I became convinced that the ancient peptides called oxytocin (OT) and arginine vasopressin (AVP), which held the evolutionary keys to reproductive behaviors and biology, might also hold keys to understanding human social and reproductive behavior – in many ways, the essence of what we imagine it means to be human [1,2]. But first, the genetics.

4.1. The journey from genes to human behavior: parsing and provisioning the human genome

The human genome is a framework for dissecting human disease and behavior. In order to ultimately understand the organization of human behavior, the self-assigned task I had begun in graduate school, I built on my fundamental premise that genetics was and would be for some time, the hub of human biology and medicine. I needed to develop the

technical and genomic tools necessary to study the human genome. When I began, chromosomes were the visible human genome, and the "Central Dogma" framed the way forward: DNA-RNA-Protein! The dawn of human genome organization had just occurred with the discovery of fluorescence-based chromosome banding using DNA-binding dyes that revolutionized cancer and illuminated a substructure of chromosomes. This ignited my belief that the human genome and chromosomes could be ordered and integrated with human behavior. This technology would lay a foundation for elucidating the nature of human development and its derangement in human disease. My first paper as a graduate student came from playing in the lab, developing novel, sensitive chromosome banding technologies that could be done in one's kitchen at a cost of pennies and using these to define the first bits of chromosomes in patients with disabilities. My goal was to solve a long-standing fundamental problem regarding how chromosomes replicated. I had no idea that science was this much fun and that the thrill of impending discovery that could help mankind was not only exciting but addictive.

The contemporary view when I began my work was that chromosome banding was unlikely to be biologically meaningful because the human genome was so large and complex (~>6 million base pairs). It was generally accepted that no consistent pattern of DNA sequences would be detectable at the level of chromosome bands. However, this assumption was actually not based on empirical evidence. This led me to embark on a series of molecular experiments to show that the human genome architecture could be differentiated at the level of chromosome bands and that, in turn, these could be dissected in appropriate human systems and related to distinct phenotypes from anatomy and physiology to behavior. More simply put, I began to search for human "syndromes" with possible genetic origins. Looking back, I can see that this required a good bit of patience and the willingness to move across intellectual and academic siloes.

During my graduate work, I was able to develop new technologies that showed for the first time that human chromosome bands were, in fact, functional units with dramatic differences in replication timing (gene and DNA content [3,4]. My early results on human chromosomes [2] became the gold standard for the emerging field of medical genetics, revealing that disruptions in chromosome 21 were the cause of Down syndrome (DS). I began to focus on DS, the most common chromosomal cause of an identifiable genetic syndrome in which I was among the first ones to molecularly show that an extra piece or whole copy (trisomy) or a missing piece-of chromosome 21 was also associated with DS (or a deletion phenotype [5]) related to a subset of DS features [2,6,7]. Moreover, 30 years before the emergence of chromosome targeting, we incorporated human breakpoints to inform the molecular cloning of an entire chromosome [8]. As chromosome 21 is also the smallest human chromosome with the fewest genes, I reasoned that DS might serve as the first human model for relating *specific* genes to human brain and behavior, a distinction held by smaller genonic disturbances [9]. And later, it was.

After these early hints and a decade of advances in human genome cloning, my own later results extended these to reveal, for the first time, the entirely surprising result that two different families of DNA sequences defined the two chromosome band types throughout the entire human genome [4]. It then took another decade of advances in human gene cloning and mapping for me to "map" the positions of the first thousand human cDNAs for genes [10,11] and simultaneously to apply this to the whole genome. In those projects, we integrated the human DNA recombination map and markers used for disease-gene hunting with the large genomic fragments that, in fact, contained the genes themselves [11,12]. Remarkably each chromosome is a vast linear highway of distinct DNA, with each gene having a specific order and address (Fig. 1) [11]. This BAC resource covered, as well as ordered, 70 % of the entire human genome (Fig. 2) [11]. This was then used to order, correct, and validate many of the whole chromosome maps generated by the international consortia patching the marvelous human genome together, one chromosome at a time. Being involved in these landmark studies was a critical step toward my larger goals.

The next mountain to climb took close to a third decade. In that work, I developed and combined novel molecular and FISH (fluorescence *in situ* hybridization) approaches and took advantage of our whole genome resource to focus on a single syndrome. The goal was to generate the physical map, identify the vast majority of genes, and begin the intense journey to *find* humans with rare genomic changes. Later, such changes would be made in rodents using genetic manipulations,

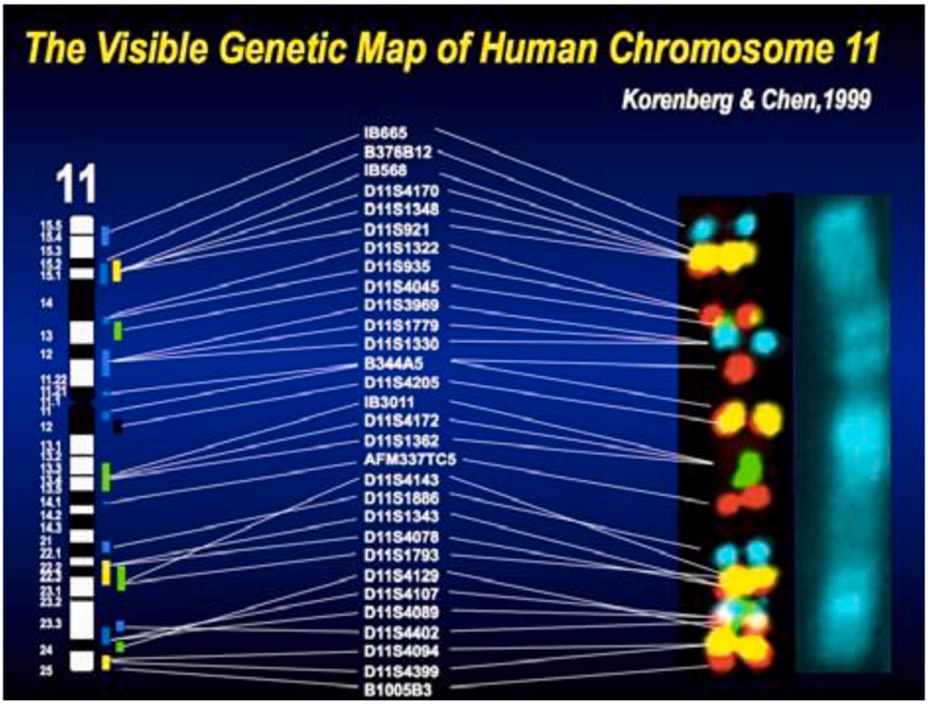

Fig. 1. Integrating Whole Genome recombination and physical maps: Combinatorial Multicolor FISH simultaneously orders and maps 27 markers to sub-bands a on a single chromosome 11 [11].

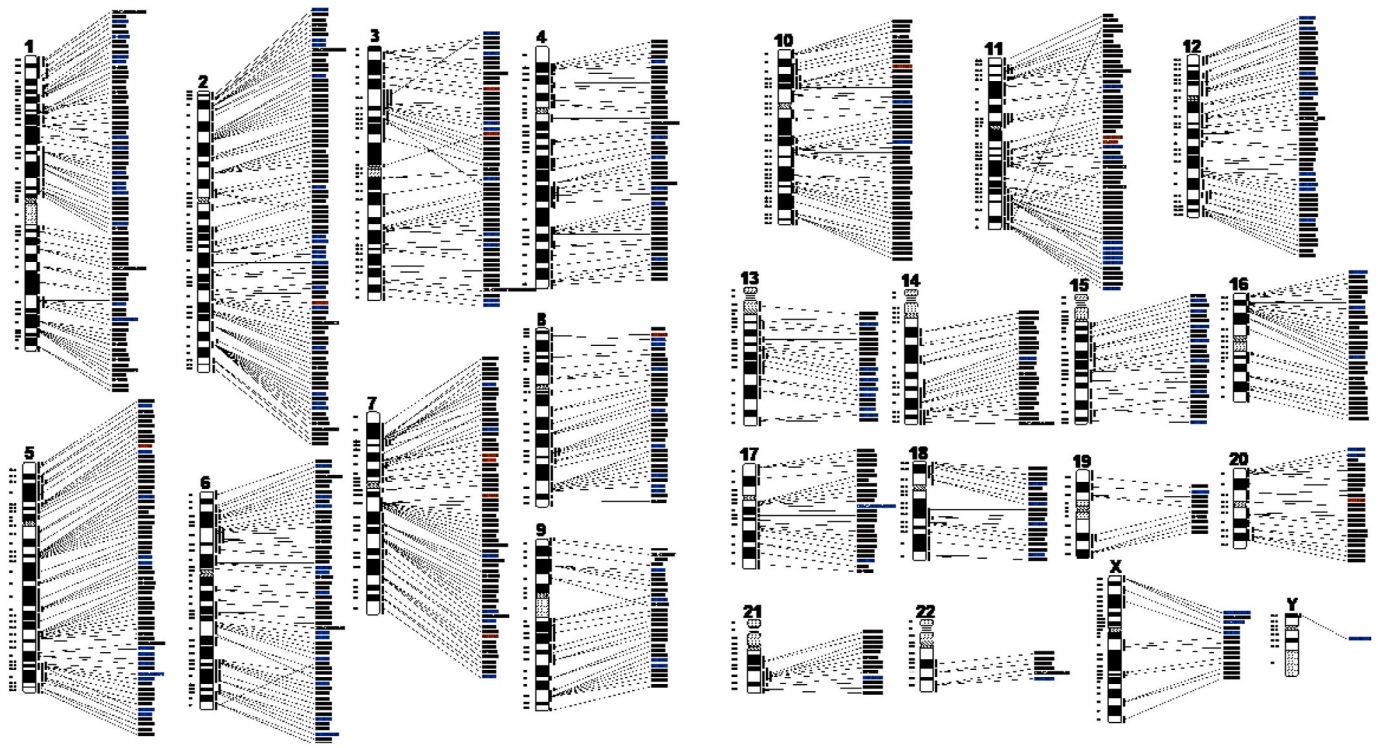

Fig. 2. Integrating human whole genome molecular and cytogenetic markers: A definitive framework linking the power of the human recombination map for defining disease Loci with the physical clones containing candidate genes [11].

but in humans, they must be found.

In summary, the centrality of using chromosome behavior for human genetics, cell biology, and development was clear, and exciting. It represented an approach for parsing human cognition, behavior, and emotion. This early work provided the critical genomic tools and approaches that would later allow identifying genetic contributions to human behavior. Along the way, we encountered solutions to questions about genome and, more recently, to human brain organization (Korenberg J, 2018) [8,13] that we had no idea even existed. Ultimately, using these tools to dissect the genetics of human models with large genomic changes would reveal a specific gene relating OT and AVP to social and emotional regulation of behavior in another fascinating genetic condition known as Williams syndrome (WS) [14].

4.2. The study of human behavior requires human models

4.2.1. Williams syndrome, the next generation: A human model for parsing genes, brain, and behavior

Again, my next journey began with an assumption that had not previously been fully tested. I reasoned that humans with distinctive cognition and emotion might carry relatively large genomic changes, such as trisomy for chromosome 21 as in DS, or duplications and deletions of smaller regions (such as those in WS). These seemed like ideal starting points for understanding the connections of genome changes with behavior. Therefore, I began by identifying and establishing the approach and analyses to define the contributions of single genes and clusters to physical features. Initially, I worked on behavior and cognition in humans with DS [2,5,12], helping to inform mouse models [15]. I then moved to the study of WS [16–18]. This ultimately allowed me and my colleagues to relate the extra or missing genetic material to the unique physical and brain features of these syndromes. These studies and an important insight from WS (described below), gave a hint that, in contrast to the expected multigenic and neural complexity of humans, some aspects of human social-emotional behavior might be unexpectedly simple. For example, WS behaviors are atypical and rather specific. In fact, WS is the only known human deletion that causes an increased drive to sociality and interest in others. It was our study of the genetics of WS sociality that led me to examine a role for OT, AVP and their receptors in social behavior in WS and in religious experience. But first we needed to examine WS.

WS is a human genetic disorder (OMIM, 194050; Williams-Beuren Syndrome; WBS) caused by the deletion of 26–28 genes occupying 1.6–1.8 Mb on one of two chromosomes 7q11.23. Occurring in ~1/7500 births, it was initially identified by congenital heart disease, SVAS (supravalvular aortic stenosis), hypercalcemia, an outgoing personality, growth, and intellectual disabilities. Further studies also revealed deficits in multiple aspects of visual-spatial construction that were later associated with structural and functional brain variants [19].

However, from my perspective aimed at unraveling the genetics of human behavior, the most fascinating features of WS were the increased drive to social interaction, particularly to strangers, interest in faces with direct social gaze, increased affect in productive language and in response to music, as well as curious, less well-studied cross-modality insights. These include observations and insights from individuals with WS - such as “music is emotional medicine” and “music is my favorite way of thinking” (Personal observations from a 42-year-old patient), or “Daddy, welcome to my world!” (Personal observation, from a 6-year-old). Of further interest were the increased regional amygdalar brain responses to happy faces, with decreased responses to fearful faces [17]. Put plainly, in contrast to IQ or growth deficits (problems that are readily measured and influenced by thousands of changes in gene copy number), these consistent WS social-emotional features are seen solely with the WS deletion of one or a subset of the 26–28 specific genes. Therefore, although copy number and/or DNA sequence variation of the remaining ~20,000 genes must contribute, the simple decreased expression of the small number of genes identified as deleted in WS genes is sufficient to produce the social-emotional phenotypes of WS. The finding greatly narrowed the genetic search and provided genetic tools for parsing both the behavior and brain circuitry. Consequently, I continue to argue that WS is an ideal model for pursuing the neural and

genetic mechanisms of human social-emotional behavior.

5. A century-old classical genetic approach to generate the finer genetic tools to parse human brain and behaviors

5.1. Paring down the genetic and phenotypic maps for social behavior in WS with partial deletions

Similar to the original work in flies showing that genetics can be used to understand behavior, in WS we could use a classical genetic approach and begin to narrow down candidate genes for social behavior in WS. This step involved generating and integrating detailed physical maps and developing ways to find rare humans with WS caused by smaller deletions; in those cases, non-deleted WS genes could inform the genetic basis of subsets of the WS social and cognitive phenotype. To do this, we analyzed 140 cases. We reasoned that smaller deletions would be associated with higher cognitive functioning in individuals in whom cognitive behaviors could then be parsed and social behavior could then be investigated (Dai et al., 2009 [19]), the premise being that the social focus and interest in strangers might be due to a small subset of genes. (Fig. 3).

At the time we began to work on this topic, there was no physical genomic map of the WS region. We, therefore, used the results of our physical map of the human genome described above [11]. Multiple surprises had arisen from these studies, including that we found multiple FISH signals near the centromere of a number of chromosomes; these identified the regions of all known human deletion syndromes, including at chromosome band 7q11.2, the position of the elastin gene, deletion of which caused SVAS (supravalvar aortic stenosis, a congenital heart problem occurring in families or together with WS). The importance of this was that elastin mapping in this region might mark a deletion that caused not only SVAS in WS but also the entire WS features, including those of social behavior. As we had already identified DNA clones [11] for more than 50 % of this region, this turned out to be correct and we showed that many of our chromosome preparations of WS in fact were deleted for these clones. The whole genome map work had been intended to accelerate the search for genes for human diseases of brain and behavior, which it did.

After analyses of the first hundred WS individuals revealed two common deletions, we found the first hints that the WS social phenotypes might be related to particular genes from two individuals with partial deletions that maintained GTF2I and/or GTF2IRD1 (e.g., Fig. 3). It is important to note here, for future reference, that GTF2I and GTF2IRD1 are two neighboring but related genes as they are derived from an ancient duplication, and both code for known transcription factors that influence some of the same cellular processes, so both may be involved in some way. Finding these genes associated with social behavior provided a way to use the genes themselves to uncover specific brain cells and structures that linked them (GTF2IRD1 or GTF2I) to the atypical behaviors seen in WS, as described below.

In fact, the two individuals with WS who had one or both of these genes revealed more typical social behaviors. GTF2IRD1 and GTF2I individuals had the more normal social drive toward strangers. In other words, one or both of these genes might be involved in WS social behavior and possibly used to identify a mechanism that was essential for the extreme sociality seen in WS. However, proving this experimentally would be another challenge. It was clearly necessary to go beyond mouse models if I hoped to identify the brain circuitry involved in something as complex as human social behavior.

5.2. Challenge #1: the giant leap from human gene candidates to primate brain circuits

5.2.1. Macaque: A surrogate brain for human brain circuitry

Therefore, the next goal was to address the major challenge posed by the vast majority of risk genes identified in large genetic studies of human brain disorders. How can one connect an unknown gene to a specific human or primate brain circuit in the most parsimonious, definitive, and rapid approach? The path was unknown and represented a common block to progress in going from candidate genes of many sources to human brain circuits. Of course, the “social brain” includes multiple nuclei and tracts. I decided to approach the problem directly,

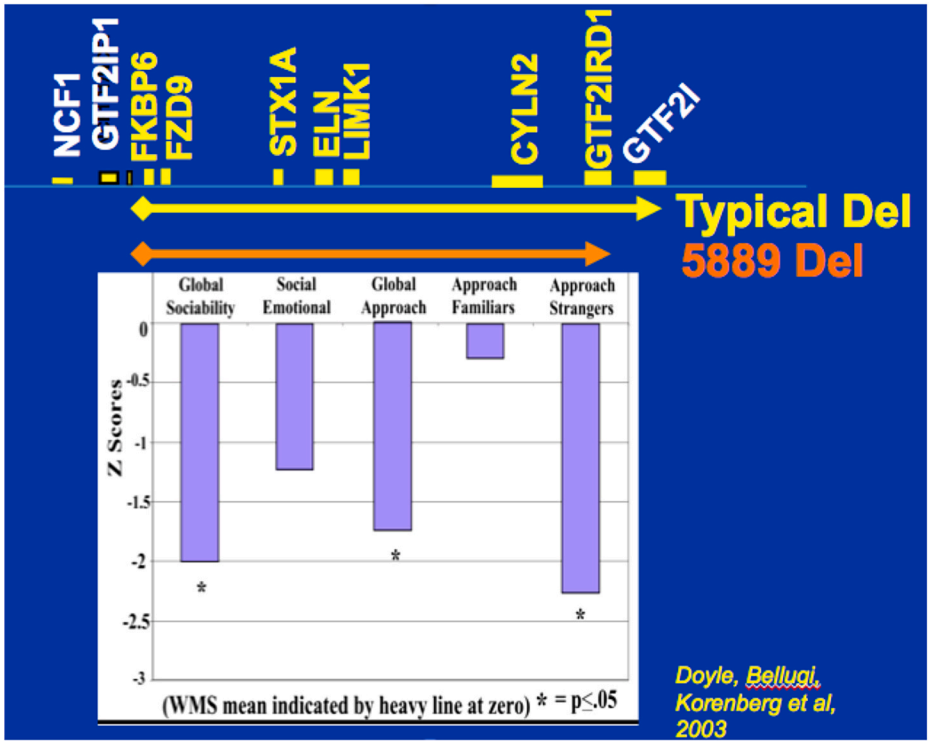

Fig. 3. WS Genotype-Phenotype Map using WS with a partial deletion implicates the evolutionarily duplicated genes GTF2I and GTF2IRD1 [20].

and to map the distribution of protein products of WS candidate behavioral genes directly on tissues from non-human primate (NHP) brains similar to the human, specifically the macaque, *Macaca fascicularis*. I needed to select a species with a brain size allowing coronal sections to fit on a 2 × 3″ glass slide, and the macaque fit the bill. The distribution of the gene's product in the brain could then be viewed through a microscope simultaneously at the axon level with neuroanatomical methods. In these studies, we also needed to generate WS-gene-specific antibodies and to combine them with multiple fiducial markers for known brain constituents and cell types, similar to the gene mapping challenges. My premise was that in the brain, protein products are generally more specific to subsets of neural cells and their projections and are more readily detectable than mRNA's. Moreover, these can be fluorescently tagged with the multiple simultaneous colors needed to represent the known structures. This was the road not taken previously because of the technical challenges, the need for novel microscopic acquisition and gene detection strategies, not to mention the exacting tissue preparation and knowledge of primate brain neuroanatomy required. However, despite the challenges, I was buoyed by my successful experience in mapping thousands of genes in colors on human chromosomes. The results of many years showed that using these tools it was possible to identify neural structures and circuits at the axon level in brain tissue sections from *M. fascicularis*. This series of studies in the macaque took a decade but was exciting because it provided the tools and approach to map not only candidate genes for social behavior, but also to determine the neural circuits for genes of a broad spectrum of brain diseases, To begin with, we focused specifically on genes that we had been implicated in differences in WS social behavior. In this case I began with the genes not deleted in individuals with smaller deletions described above. In other words, the two gene(s) found in individuals with WS who did not have a deletion of GTF2IRD1 and/or GTF2I. These individuals had other physical features of WS but did NOT have the WS behavioral phenotype of atypical social behavior (see Fig. 3 for an example of deletion sparing GTF2I).

We hypothesized that protein tags for two proteins, GTF2I and GTF2IRD1 encoded by genes from the WS region associated with altered social behavior, would generate a specific pattern of expression. The location of these gene products might reveal specific brain circuitry that could be identified as having known neurobiology in the mammalian brain.

The results were dramatic (Korenberg in preparation). As predicted, the antibody for the proteins encoded by GTF2IRD1 and GTF2IRD1 stained the nucleus of most glia and neurons in the brain. But what was entirely unexpected, the antibody to GTF2IRD1 also brilliantly stained the entire cell body as well as dendritic and axonal projections of the magnocellular and parvocellular neurons of the PVN (paraventricular nucleus of the hypothalamus) (Fig. 4 illustrates OT and AVP in the macaque PVN; Korenberg, in preparation). The PVN is a brain region with a well-established role in mammalian social-emotional regulation. Even more remarkably, the PVN is a major site for the synthesis of OT and AVP. However, it would require five years of subsequent experiments to determine whether GTF2IRD1 colocalized with an unknown subset of magnocellular neurons or whether we had identified a WS gene that colocalized with either class of magnocellular neurons expressing OT or AVP. This novel localization of GTF2IRD1 could be a critical clue to the regulation of sociality and the atypical sociality of WS.

The localization of GTF2IRD1 in the PVN suggested that GTF2IRD1 might be regulating OT or AVP, which in turn might bind to OT and OT and AVP receptors (OTR, V1a, and V1b). Previous studies in other models had established that both AVP and OT can bind to the others' receptors and projections of either might mediate both receptor classes. Armed with the tantalizing knowledge that in a primate, GTF2IRD1 localized in the PVN, it was still possible that the colocalization was fortuitous. Furthermore, perhaps neither OT and/nor AVP were misregulated nor related to social behavior in WS.

Around this time, the mouse OT knockout was shown to have altered social behavior. This engendered a frenzy of untested WS behavioral hypotheses. However, our data had revealed one of the most puzzling, but exciting observations; that, in contrast to the primate, neither the mouse nor the rat brain limbic system projections or PVN cytoplasm stained with the antibody to GTF2IRD1. Although this may have been due in part to a lower cytoplasmic concentration, the lack of GTF2IRD1 signal in the rodent versus the primate PVN also suggested that aspects of the mechanisms regulating human and primate social behavior, differed in the rodent. Moreover, to the extent that GTF2IRD1 localization to the OT-AVP magnocellular neurons of the primate PVN was related to WS-like sociality, this mechanism could not be readily modeled in the rodent. That is, the genes related to social behavior in WS and localized to the PVN OT- AVP region of a primate might not have the same role in the mouse or rat. This should not have come as a surprise. Therefore, given the not so subtle differences in mouse and human social behavior, our next step was not to return to a rodent model, but to determine whether either OT or AVP levels differed in any way or were related to social behavior in persons with WS.

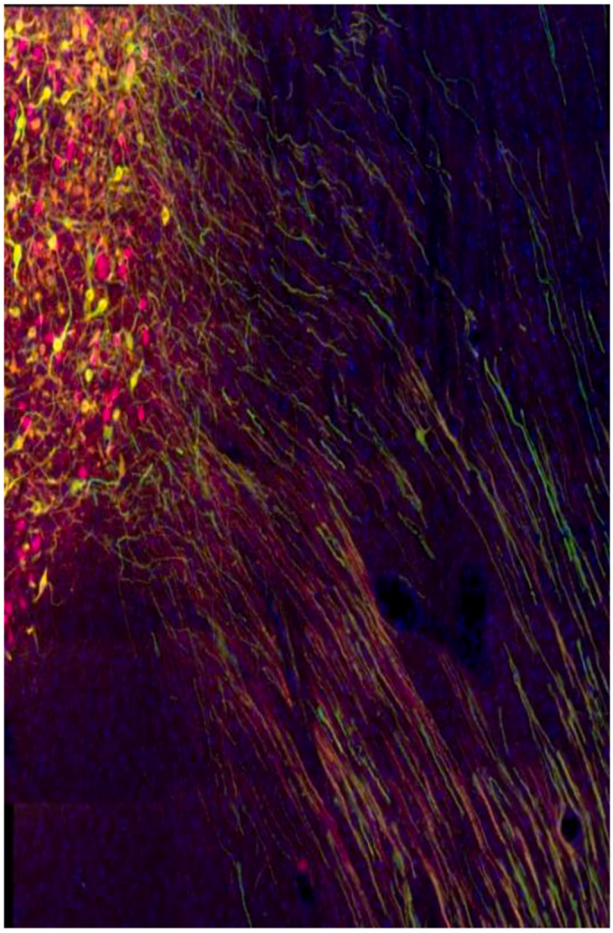

Fig. 4. Image of OT (red) and AVP (green) neuropeptides in the macaque PVN using immunohistochemistry. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

5.3. Challenge #2: OT- AVP results from model systems must be confirmed in humans

Hypotheses are useful, and our data were encouraging, albeit not exactly what we predicted. Of course, they opened a number of new avenues of study. In chasing the genetic and neural circuits for human socio-emotional behavior, it was critical to empirically demonstrate the involvement of OT and AVP in WS. We used music as a social stimulus

and a cold pressor as a physical stimulus, and found, as we predicted based on GTF2IRD1 expression in the PVN, that OT and AVP levels both differ significantly at baseline, when individuals with WS were compared to age and gender matched typical controls (TC) (Fig. 5) [21]. Moreover, in a principal components analysis, the OT and AVP levels correlated positively with the tendency to approach others and negatively with adaptive (high OT with decreased adaptive) and maladaptive (high AVP with increased maladaptive) behavior subscales on the Scale of Independent Behavior-Revised (SIBR) (Fig. 6).

Three questions were addressed by these results. First, although the differences in measured OT-AVP levels in WS are unidirectionally increased, some by $>$ 100 fold[8], it was not possible to conclude that increases in OT or AVP are the "cause" of WS positive social behavior. Nor is it known exactly which OT or AVP related moieties are being detected, since these studies were conducted using an antibody-based enzyme immunoassay (EIA). However, what could be inferred is that in WS, there is a striking disturbance of the social neuropeptide system related to both OT and AVP and/or their receptors [21]. Third, although the measured levels of OT and AVP appeared to respond to the social/emotional stimulation of music and the physical stimulation of cold, the correlation with both social/emotional stimuli could be detected even using only the baseline levels (without specific stimulation) This suggested that the variation in OT or AVP was related more to a constant state of the individual, possibly reflected in part by DNA sequence variants of OT, AVP or their receptors. With the above caveats, the results of studies of WS and controls in response to music or cold clearly established that the OT-AVP system was disturbed in WS and the perturbations at baseline, even in the absence of a provocation, correlated with social behavior in WS.

In summary, working exclusively with primates, using the *Macaque fascicularis* brain as a surrogate for the human brain, but *not* human behavior, the multidisciplinary results from seven focused and independent hypotheses ultimately led from genes to brain and behavior, and back. At every step, this necessitated the development of novel technologies and tools applicable to a broad spectrum of human behavioral disorders. The studies using these methods allowed us to.

1. Generate a genomic physical map of the WS 7q11.2 deleted region.
2. Identify rare individuals with smaller WS deletions, and to refine their genetic breakpoints using the genomic map.
3. Identify deletion of a specific WS region gene, GTF2IRD1 associated with tests of social behavior in WS with partial deletions; this suggested a path forward using gene specific antibodies to GTF2IRD1 to determine if specific brain systems expressed the protein, in this case using 2000 high resolution microscopic images of an entire macaque brain section.
4. Discover that the GTF2IRD1 protein product specifically identified the primate hypothalamic PVN (paraventricular nucleus) circuits and limbic projections in macaques, using multiwavelength fluorescence immunohistochemistry (IHC).
5. Establish a neuroendocrine system relevant to sociality in primates by localizing the WS region GTF2IRD1 protein (implicated but not established in WS without deletion of one or both of the two related genes (GTF2I and GTF2IRD1)) in the primate hypothalamus, specifically expressed in the magnocellular neurons of the PVN.
6. Validate our hypothesis from macaque brain that peripheral OT and AVP neuropeptide levels would be abnormal in WS and specifically,

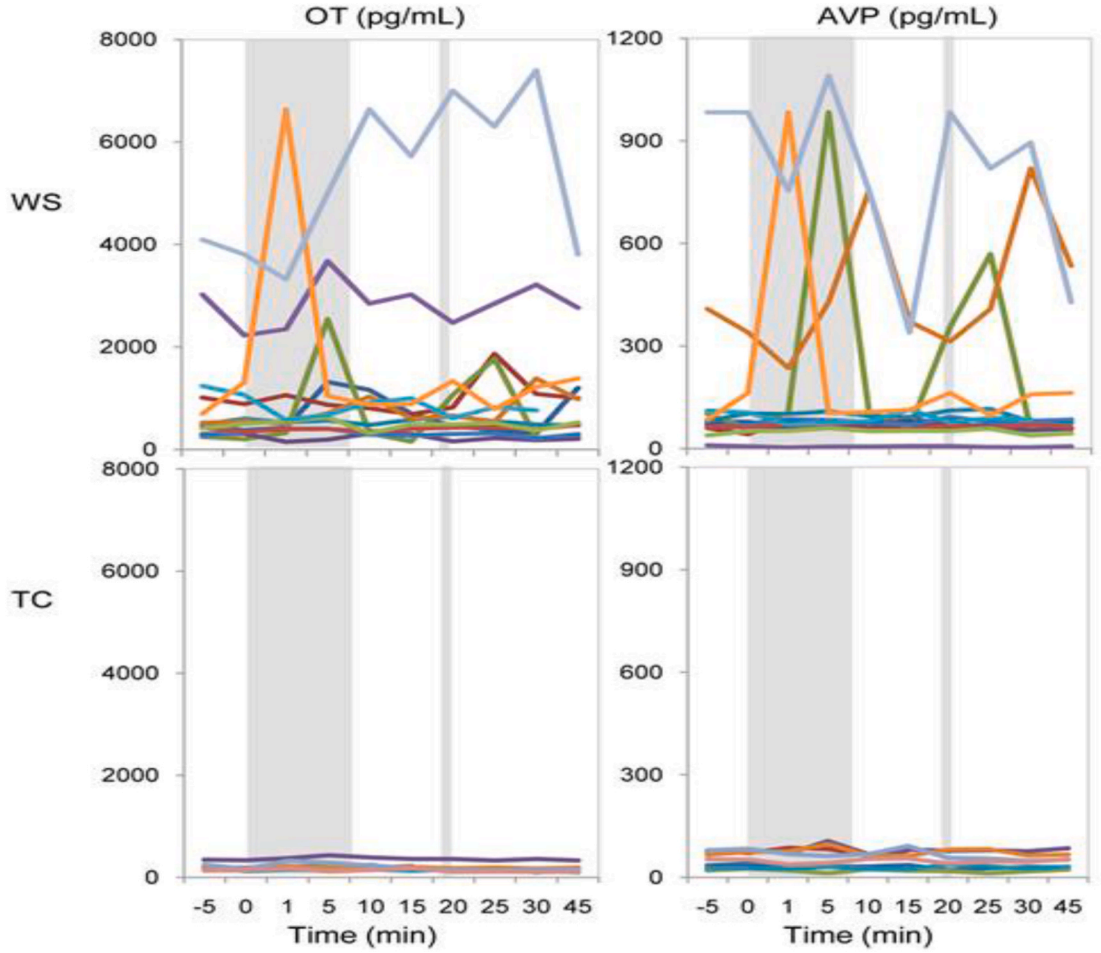

Fig. 5. Plasma OT and AVP are 100–1000 X elevated in Williams Synndrome (WS) versus typical controls (TC), age and gender matched [21].

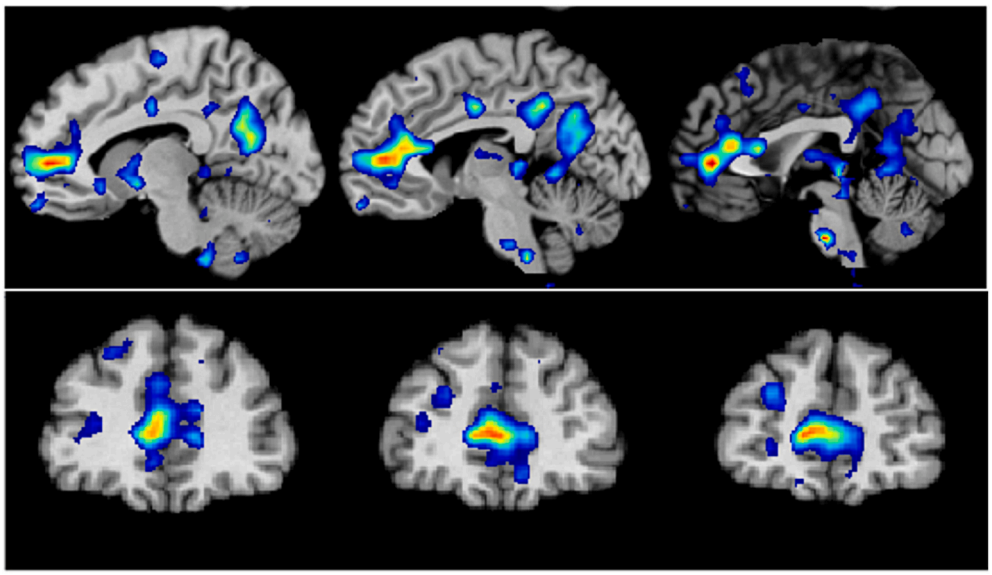

Fig. 6. fMRI showing brain regions, active during self-report of "feeling the spirit", that are correlated with plasma OT in religious individuals. Note the highly active Ventromedial prefrontal cortex (vmPFC) and Anterior cingulate cortex (ACC) (Korenberg et al., in preparation).

7. Show that both OT and AVP are dysregulated at baseline in WS and both begin to increase within 30 s in response to emotional and/or physical stimuli,
8. Establish that the baseline levels (not necessarily the stimulated levels) of OT/AVP correlated with WS behaviors. Taken together, the results implicated a disruption in the baseline state of the hypothalamic limbic system associated with OT and/or AVP was associated with social behavior in WS.

In conclusion, the results above established that the OT-AVP system was dysregulated and related to social behavior in WS. Moreover, the WS deleted gene, GTF2IRD1 colocalized at subcellular resolution with neuropeptides in the magnocellular neurons of the primate limbic system, specifically in the PVN. Our subsequent work revealed GTF2IRD1 also colocalized in the OT-AVP neurons of the primate medial preoptic region (Korenberg, in preparation). This was of interest because in rodents the medial preoptic region is associated with maternal behavior.

These results were followed by subsequent neural imaging in WS [22]. In those studies, we were able to show increased fMRI activity in the amygdalar region (a target of PVN OT) when the subjects were shown happy faces, and decreased activity when presented with fearful faces. Taken together, our data converged on a central regulatory role for endogenous OT and/or AVP in WS socio-emotional behavior. These findings implicated the possible involvement of the hypothalamus and GTF2IRD1 in regulating social neuropeptides in WS. The plot was thickening.

In order to generate the above results, we followed a few general principles.

I. *Know your organism.* Crucial human insights came from observing the distinct, "positive" social-emotional behavior in a consistent genetic condition, in this case WS, followed by elucidating its physical genomic map. Then, to parse the genetic contributions, it was necessary to establish well-defined measures of social behavior sub-phenotypes. This method, beginning with a phenotype and working backward to the gene, was a variant of the classic genetic approach used 100 years ago to find genes in flies, corn, and then mice. However, there is one major difference between these model systems and studies aimed at humans: the mutations can be made in these models, but in humans, *they must be found.*

II. *Sometimes, intelligent brute force is useful.* Therefore, to find atypical deletions of WS and facilitate sorting through the 25–28 typically deleted genes in WS that might contribute to a behavioral subtype, we developed behavioral criteria, (such as IQ above the range of WS) to maximize finding WS with atypical deletions. The goal was to find WS with deletions that did not include all genes and were not manifest for all social phenotypes. This approach identified GTF2IRD1 and GTF2I. (We note that these genes are a minimum; others could also contribute to WS social behaviors.)

III. *Don't give up.* The next step - identifying, not simply speculating on (from model systems) the primate brain system mediating the function of a candidate gene - it was necessary to develop novel technologies. In this case, we developed high-resolution multicolor fluorescence-based immunohistochemistry in primate brain sections and then used this method to drill down to the axon and cellular level. In a somewhat humorous turn of scientific events, after celebrating the beautiful result nailing GTF2IRD1 in the PVN, at the center of social regulation by OT-AVP, we discovered that there were no microscope systems in existence that could acquire fast enough or manipulate the enormous datasets that were necessary to share the startling informaiton in the high resolution multicolor images that we were viewing! This included discussions and hundreds of hours of testing generously provided, hardware and software together with technical experts from Zeiss, Leica, Nikon, and multiple innovative startups. The problem was emphasized in a talk with the CEO (founder, chief executive officer) and CSO (chief scientific officer) of a top microscope imaging company, who opined tolerantly, "Dr. Korenberg, what you are asking would take more computing power than exists in the world at present." Their next statement was "We are writing a grant to do this." My response was simply that we needed to think differently about how to achieve the goal. However, an equally humorous, if frustrating, response came from scientists (and administrators) outside the field who looked at what I was doing and said, "Hasn't that been done already?" No, it hadn't, and we did it, but this is the subject of a different chapter in my career. Our existing imaging systems produced beautiful images that unequivocally established the localization of the WS gene GTF2IRD1 in the magnocellular neurons of the PVN of primates.

IV. *Match the model system to the question.* Importantly, we noted that the macaque and human neural systems for socio-emotional behavior were highly homologous and measurable at the neuroanatomic level in subcortical pathways previously implicated in regulating social behavior in various mammals. The critical point here was to focus each approach on the organism and neurobiological system that was capable of answering a specific question and not to equate human behavior or gene actions with that of other species or cells until these assumptions were proven. Therefore, we used humans to determine both the behaviors of interest and the genes associated with them. Once a human gene is known to influence a human behavior of interest, non-human and cellular models can be used to dissect the mechanisms and modifications.

The WS partial deletions had focused us on a specific gene, but we had no idea what human or primate brain system this gene might be related to; this is the classic central question of most GWAS results, and there are still few ways to answer this question. Therefore, the next key experiment required the generation and use of antibodies to the protein product of the WS region gene (GTF2IRD1) and its use to identify a homologous neural system in the eight-fold smaller macaque brain. This took 4 years and the kind help of David Amaral, who generously supplied the first superb sections of the macaque brain. Our neuroanatomic localization of GTF2IRD1 in PVN magnocellular neurons was critical in leaping from a "risk" gene to a study of the primate OT-AVP brain neuroendocrine system. It was then critical to validate our consequent hypothesis that the OT-AVP system was dysregulated in WS. Therefore, we developed and applied a paradigm using music and a cold pressor in WS and in typical control subjects [21]. In that study we simultaneously determined OT and AVP levels which, as noted above, differed significantly in WS (Fig. 5) and were related to social behavior [21]. We note that the colocalization of GTF2IRD1 with the cells expressing OT or AVP in the PVN, strongly implicated the likely involvement of the WS gene in regulating the OT-AVP system and WS and possibly non-WS sociality, but did not prove it.

The gift of a human model such as WS is that this mechanism involving GTF2IRD1 can now be studied. Moreover, during this period, evidence for the OT-AVP system was accumulating. Documenting a role for GTF2IRD1 in the OT-AVP system and human sociality might have to wait. Rather, the more pressing challenge was to address the brain circuitry that mediates the socio-emotional experience and behaviors seen in WS; a circuitry that appeared to be related to OT-AVP. The results with WS provided strong support for this next step, which was to determine whether this WS gene might help us link the OT-AVP to the capacity of the human nervous system for both sociality and spirituality.

5.4. Challenge #3. Moving from the novel traits of WS to the study of spirituality and the "religious brain."

The next, challenge would be to link OT, AVP and cells regulated by the gene associated with WS (GTF2IRD1) to human brain activity. Most of my academic career in medicine had been conducted at the University of California, Cedars-Sinai in Los Angeles, where my research had faced the challenge of translating the flowering chromosomal knowledge [4] to genomic insights and practical tools blanketing the whole human genome [10,11]. During this time, two further threads essential for understanding humans were interwoven with genetics; rodent and primate neuroanatomy, and measures of human emotion and behavior. After years of making and validating highly specific antibodies and taming technical issues around studying primate brain fluorescence, we had documented the fact that the WS GTF2IRD1 protein product localized in OT-AVP neurons specifically in the PVN, a hypothalamic center integrating autonomic and neuroendocrine aspects of behavior and emotion. The excitement around this finding led to hundreds of IHC experiments to validate it, and the hope that the GTF2IRD1-OT-AVP circuit might lead to a mechanism for the partly anecdotal increased "compassion" and spirituality of WS. Not entirely tongue in cheek, we envisioned the possibility of modifying behavior acutely with a "nasal spray for compassion".

An opportunity to continue toward this goal arose in 2007, when I was offered a Professorship to direct a new cluster, "Circuits of the Brain" in USTAR (Utah Science, Technology and Research) at the University of Utah as well as Directorship of a center for Integrated Neuroscience and Human Behavior. In Salt Lake City, I teamed up with an imaging colleague, J. Anderson. I extended my search to understand the "social brain" to also include the "religious brain", and specifically the possible role of the OT-AVP system in both.

This move to study spiritual experiences was driven in part by my lifelong fascination with the biology of the divine. It also was grounded in the general assumption that various brain regions and connectivity associated with "the social brain" are implicated in a broad spectrum of interactions with others. My specific intent was to use the knowledge gained from the genetics and neurobiology of WS as a guide to the neural and endocrine systems involved in both social-emotional experiences and spirituality. Simply put, I asked …"Could the same neural circuitry that mediates our relationship to others, also be involved in our relationship to and love for God?"

6. Obstacles and solutions: from social neuropeptides to the "religious brain."

The goal of understanding our "religious brain" was similar to the search for the neuroendocrine basis of brain regions associated more generally with the regulation of socio-emotional behaviors. This had begun with observing, from research in many species, that such regions were associated with specific peptides, especially OT and AVP [1]. The explosion of mapping of neuropeptides such as AVP and their receptors to several brain regions in a vast array of mammalian species helped to support the concept of a "socio-emotional brain" [23]. However, not all regions of "socio-emotional brain" were sites identified by OT-AVP or receptor mapping, and the same would be expected for brain regions active during religious experience. In fact, for more complex responses, brain areas regulated or influenced by OT or AVP may not have visible OT or AVP projections or even express receptors for either OT or AVP [24]. At present, it remains unclear which specific brain regions, or human socio-emotional behaviors, are regulated by OT-AVP and their receptors. Therefore, I felt it was important to go beyond the localization of OT-AVP peptides and receptors to ask in humans which specific brain regions might be activated by, or at least correlated with, levels of OT-AVP and their receptors.

I began to look for a way to test the hypotheses arising from my work in WS that seemed to relate OT-AVP and their receptors to patterns of exceptional sociality. To understand this system and to relate it to spiritual experiences, I felt it was necessary to move from animal models, or even the uniqueness associated with WS, to the study of more typical humans. I needed to find individuals who might have exceptionally strong spiritual and social experiences. Being in residence at the University of Utah, I had the opportunity to collaborate with Jeffrey Anderson, a colleague using brain imaging to study reliogious experience in devout Latter Day Saints (Mormons), who had recently completed a two-year religious mission [25]. During this experience, learned spiritual practices influence the emotional experiences of these missionaries. Missionary training and practices might be seen as a kind of naturalistic experiment around the emergence of a "religious brain."

It is well known in many species that socio-emotional behaviors involve neural input from multisensory environmental stimuli that are processed in part by subcortical regions. Social stimuli, in turn, may directly or indirectly target cells containing OT, AVP, or their receptors; these, in turn, project from the hypothalamus to cortical regions, where meaning is assigned and integrated with other complex responses. However, at present, it still remains unclear which specific brain

regions, or human socio-emotional behaviors, are regulated by OT/AVP and their receptors. The effects of OT and AVP are mediated not only by direct axonal projections to specifically distributed receptors but also by the electrical/chemical downstream circuitry regulating other regions, including the cortex. Therefore, these areas nonetheless may be regulated by OT and/or AVP and may be detected by correlation with peripheral OT or AVP levels and/or variants in their receptors. Consequently, the critical question for understanding the neural circuitry of social-emotional behavior requires simultaneous outcome measures of behavior, OT and AVP peptide expression and brain activity, in the context of specific experiences. In this case, we focused on what is called "feeling the spirit."

Thus, the larger experimental question was - could we identify human brain regions that might constitute a "spiritual or religious brain" and, could these be related to the OT-AVP system? To begin this work, my colleagues initially determined brain regions, as measured by fMRI BOLD signal, that were correlated with "feeling the spirit" in response to spiritual/religious stimuli [25]. Our next goal was to determine whether a subset of these regions might be related to individual differences in OT or AVP. We also used measurements from this study to compare the activation of specific brain regions while the individual self-reported "feeling the spirit," correlating these with individual blood levels of OT and AVP, and the DNA sequence variants of their receptors, the OTR and V1a. The established DNA variants were included to provide a way to determine whether the activations of particular brain regions while "feeling the spirit" might be related to the OT-AVP system independently of whether these resulted in changes in neuropeptide levels. This approach expanded the definition of brain regions involved in religious experience [25] to implicate the neurobiological system that might regulate the experience,. Therefore, regardless of uncertainty as to the precise neurochemical mechanism or form of OT or AVP, the paradigm could capture the involvement of the OT-AVP system, even if OT or AVP did not change acutely during the religious or spiritual experience.

In summary, having shown in WS, that OT and AVP differed from controls and that the levels were in part related to the individual's social behavior, these next experiments looked at what was in the black box, the brain regions that translated the peptides and receptors into feelings.

6.1. The religious brain: an emerging frontier for OT, AVP and their receptors

The results from the experiments that followed are preliminary. They are referred to here before formal publication as they suggest the possibility that a subset of the fMRI BOLD signals observed while "feeling the spirit" may be related to the OT-AVP neuroendocrine system. The most striking finding was that, in general, the brain areas activated while "feeling the spirit" were regions that were correlated (in preliminary analyses) with the OT-AVP system. These brain areas overlapped with those previously implicated in social behavior using multiple paradigms. It was immediately tempting to consider how and why the "social brain" might have informed or been a necessary precursor to the emerging concept of the human "religious or spiritual brain".

One example of possible further interest is our finding that the activation of the nucleus accumbens [25], a center associated with the reward system in rodents, did **not** appear to be as strongly related to OT-AVP as it was to the overall activation pattern. This suggested that "feeling the spirit" might involve multiple systems and components that were not solely reward-related.

Specifically, although preliminary, Fig. 6 illustrates one of a subset of regions associated with the OT-AVP system measures. As another example, the ventromedial prefrontal cortex (vmPFC) - anterior cingulate cortex (ACC) had previously been shown to express high levels of activation when people reported "feeling the spirit" [25]. Important for this work is the finding that, in previous studies with different paradigms, the vmPFC had been related to social interactions as well as self-insight, integration of self with others [26], and issues of moral importance. Moreover, the development of "Self-Other" (conducted in previous studies in children) had been related to the change from dependence on the caregiver to an awareness of "other," and was particularly associated with the development of the paracingulate regions [27]. We note that the OT-AVP system had been associated with vmPFC in voles [28] and humans [29], further supporting a role for OT-AVP in circuitry for both social and potentially religious experience.

Therefore, the preliminary association of OT/AVP measures with activity in the vmPFC/ACC during "feeling the spirit," rather than with the nucleus accumbens reward system (more typically associated with addiction, sexual excitement, and birth), suggested that OT-AVP and receptors in the vmPFC/ACC, might also be instrumental in mediating the more abstract concepts of social interaction related to "self-other", such as one's relationship to a higher power.

Discovering the neurobiology that allows us to seek "God" and be uniquely human remains ongoing. For now, I can only speculate that the regions associated with OT-AVP that we saw activated by imagery and "feeling the spirit" appear to involve the default mode network [30] and the "social brain". The data suggest that these same systems for social interactions might also be involved in aspects of higher-order social--emotional functions involving values and moral judgement, such as those related to a higher being.

Here, I digress from empirical research and my ongoing personal journey to observe that there may be interesting parallels between what we have found in observant Mormons, WS patients, and other primates with maternal care of the young. C. S. Lewis. Lewis noted in *The Screw Tape Letters 1942* [31] that the romantic attraction of a couple that leads to reproduction in some way is transferred to the care of the young. And, although perhaps not as evident to Lewis or to Martin Buber [32] the latter's fundamental characterization of the religious sentiment as distinguishing and perceiving a "thou" versus an "It", regardless of whether the "other" was a partner or a tree, perhaps the "self-other" brain system is fundamental, not only to socio-emotional behavior but also to one's spiritual life. That is, one might imagine that the concept of "God", regardless of any specific religion or culture, is the ultimate "Other" with respect to the brain system used to understand and experience the mature religious state.

It is important to note that this proposal does not distinguish or involve any given external "God", features or relationship, but only that humans use parts of the brain and relevant hormonal systems, that are likely shared by all people, to experience "God", a form of higher power beyond our physical knowledge. This requires the abstraction sophistication of the human prefrontal cortex. Although multiple emotional and behavioral aspects are seen in other animals, the more advanced concepts and attributes of self-other and abstractions of past and future are seen only in humans. For each culture or religious group, children and other new community members learn and must integrate an understanding of "God" into their mature emotional and spiritual lives.

In summary, I suggest that a curious combination of evolution - including the early formation of social groups seen in many organisms, through the development of social hierarchy seen both in groups and within families - may have in some way set the stage for the subcortical emotional systems essential for tying the pleasures of religious experience, its regulations, and hierarchies to the abstraction of "God". But thus far, only humans have the highly integrated and powerful abstraction afforded by the relatively recently developed prefrontal cortex required for the ultimate moral other, which we call "God".

Our place in the universe would appear to be quite diminutive when compared to the unknown expanse beyond our knowledge. It is not novel to suggest that the primate nervous system and OT could be essential components of the human capacity for religion and morality [1]. However, the details and implications of this hypothesis remained largely untested. In addition to technological advances beyond time, our very existence may depend on understanding this concatenation of social behavior on earth with our view of "God" as a higher good.

The search for "God" has much left to teach us about our complex experiences throughout life and what we may still have to grasp in order to fulfill the higher-order values of what it means to be human.

6.2. Science is a meaningful, spiritual and joyful pursuit: a few thoughts for success

Write, you are not alone.

Mentors, the good, the great, the bad and the ugly. It is about the match.

Celebrate every advance with joy.

Gratitude to self and others is a healthy practice. Integrity is paramount.

Creativity can be a lonely place. Find those who understand.

Write, it gets easier.

7. Training and mentoring

"Tis a gift to come down where you ought to be": Training is the blessing of those who embody passion and awe, who openly share joy and uncompromising integrity and who see and accept you with grace and understanding. The author was blessed at each of the following steps acquired her BSc in genetics, divinity and psychology at McGill University, her PhD in Genetics and Chromosome-Genome architecture (Klaus Patau, Eeva Thermann-Patau, Oliver Smithies), the Woods Hole Course on Embryology (Eric Davidson/Victor Hamburger), Medical Genetics with Renata Laxova, and early collaboration with Samuel Latt (Harvard Medical School), followed by a Post-doctoral fellowship in High Voltage Electron Microscopy (Hans Ris) at the University of Wisconsin Madison. This was followed by her MD in the NIH supported experimental PhD-MD Program at the University of Miami, Internship and residency at the Harvard Boston Children's Hospital and post-doctoral fellowship in molecular genetics of Cystic Fibrosis (Harvey Colton). Formal post-doctoral fellowship in Clinical Genetics at UCSF (University of California, San Francisco) (Charles J. Epstein) set the stage to integrate basic contemporary biology and genetics toward the understanding of human development, brain and behavior.

Figures

1. Integrating Whole Genome recombination and physical maps: Combinatorial Multicolor FISH simultaneously orders and maps 27 markers to sub-bands a on a single chromosome 11.
2. Integrating Human Whole Genome Molecular and Cytogenetic Markers: A Definitive Framework Linking the Power of the Human Recombination Map for Defining Disease Loci with the Physical Clones Containing Candidate Genes [11].
3. WS Genotype-Phenotype Map using WS with partial deletions (one shown) and normal range sociality, implicates the evolutionarily duplicated genes GTF2I and GTF2IRD1.
4. Image of OT (red) and AVP (green) neuropeptides in the PVN of *Macaca fascicularis* using IHC
5. Plasma levels of OT and AVP are 100–1000 fold elevated and related to social behavior in Williams syndrome [21].
6. OT-AVP correlated brain regions active when "feeling the spirit": The "Religious Brain" hitches a ride on the "Social Brain".

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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