Oxytocin

Received: 17 May 2021 | Revised: 25 June 2021 | Accepted: 10 July 2021

DOI: 10.1111/jne.13014

EDITOR INVITED REVIEW

Journal of Neuroendocrinology WILEY

Oxytocin: A citation network analysis of 10 000 papers

Gareth Leng[1] | Rhodri I. Leng[2]

[1]Centre for Discovery Brain Sciences, University of Edinburgh, Edinburgh, UK

[2]Department of Science, Technology and Innovation Studies, University of Edinburgh, Edinburgh, UK

Correspondence
Gareth Leng, Centre for Discovery Brain Sciences, University of Edinburgh, Hugh Robson Building, 15 George Square, Edinburgh, EH8 9XD, UK.
Email: Gareth.leng@ed.ac.uk

Funding information
Economic and Social Research Council (ESRC)

Abstract

Our understanding of the oxytocin system has been built over the last 70 years by the work of hundreds of scientists, reported in thousands of papers. Here, we construct a map to that literature, using citation network analysis in conjunction with bibliometrics. The map identifies ten major 'clusters' of papers on oxytocin that differ in their particular research focus and that densely cite papers from the same cluster. We identify highly cited papers within each cluster and in each decade, not because citations are a good indicator of quality, but as a guide to recognising what questions were of wide interest at particular times. The clusters differ in their temporal profiles and bibliometric features; here, we attempt to understand the origins of these differences.

KEYWORDS

bibliometrics, history, hypothalamus, neuropeptides

1 | INTRODUCTION

In 2002, Gainer et al[1] described the hypothalamic-neurohypophysial system, comprising the neurones that secrete oxytocin and vasopressin from the posterior pituitary, as "a veritable 'Rosetta Stone' for neuroendocrinology and neuroscience". Amongst the "many seminal findings" that came from this system, they highlighted the discovery and characterisation of neuropeptides,[2] the development of peptide agonists and antagonists,[3] the proposal of the prohormone concept,[4] the characterisation of bursting pacemaker activity in central nervous system neurones,[5] and the demonstrations of neuropeptide secretion from dendrites,[6] of glial-neuronal plasticity[7] and that peptides can produce complex behaviours.[8]

We felt prompted to ask whether this system might also be valuable for understanding *how* scientific understanding develops. We sought to trace how knowledge about oxytocin has changed and is changing, and how that understanding varies in the works of different scientists pursuing different research objectives. To do this, we use a systematic search to capture a large part of the oxytocin literature, and we use citation network analysis to identify its structure, clustering papers according to their citation links.

We begin with a brief account of the beginning of the oxytocin field. We then analyse each cluster to identify its topic focus, and show how the field has evolved since 1950, using bibliometric data to identify highly-cited papers. We do *not* assume that high citation counts define the best papers, but only that they indicate the changing foci of scientific activity. By this, we sketch out an outline of a history of oxytocin research – of the different perspectives of what oxytocin is and does, and what some might hope it might do. Our aim is to provide a sense of the diverse research questions, ideas, and findings that have motivated, and continue to motivate, research on oxytocin. And, by examining the publication and citation dynamics of this field over the last 70 years, we hope to help the reader to better understand the publication and citation metrics that continue to pervade and distort academia.[9]

2 | METHODS

Oxytocin was the first peptide hormone whose sequence was established, and the first to be synthesised; its gene was amongst the first mammalian genes to be sequenced,[10] and it has been a

medicine of major importance for at least 70 years. We thus anticipated that many papers for which "oxytocin" is particularly salient would mention it in the title. To collect these, we searched the Web of Science (WoS) Core Collection (SCI-EXPANDED 1900-, SSCI 1900-) for papers with the terms "oxytocin" OR "Pitocin" OR "syntocinon" in the title; these, we henceforth call 'OT papers'. The final dataset comprises documents published by the end of 2020 as recorded by 1 February 2021. The search returned 15 375 documents, while a 'topic' search of the titles, abstracts and indexed keywords returned 29 604. Whereas 'oxytocin' in the title consistently reflected a focus on oxytocin, many papers for which oxytocin was only a 'topic' had little association with oxytocin. For example, the most highly cited 'topic only' paper, with 1847 citations, has the title 'ER beta: Identification and characterisation of a novel human oestrogen receptor'; 'oxytocin' does not appear in the abstract and only once in the whole text.[11] We therefore used only papers retrieved by the title search, and restricted the results to documents published in English (as categorised, sometimes erroneously, by WoS), then to papers classified by WoS as 'articles' or 'reviews', (ie, excluding abstracts, book chapters and conference proceedings). We based a pilot study[12] on articles alone, but the distinction that WoS makes between articles and reviews is extensively erroneous, and here we disregarded it. This reduced the set to 10 676 OT papers. All bibliographical data recorded by the WoS for these were downloaded, including the reference lists. Although OT papers cite, on average, 16 other OT papers, the broader citing literature (approximately 89 000 papers) cites an average of just two. So, despite the simplicity of our query, we managed to capture a densely interconnected literature.

From these data, we constructed a network in which (in the language of graph theory) papers are *nodes* and citations links between papers are *directed edges* between nodes (ie, the links have a 'direction, from a citing paper to the cited paper). We extracted all references from all papers, linked unique references to numerical identifiers and stored this information in an 'edge-list' that records the citations from paper *i* in a 'Source' column to paper *j* in a 'Target' column. We also constructed a node attribute list, which includes the numerical identifier that corresponds to the identifier used for the edge-list, and data on authors, year of publication, article title, journal of publication, total citations, total reference list size and WoS accession number. These data were cleaned to merge references duplicated by variants in format or referencing errors, and restricted to papers retrieved via WoS for which we had full data. We analysed these data in Gephi 0.9.2,[13] visualising networks via the ForceAtlas 2 algorithm that clusters nodes together that are densely interconnected.[14] We partitioned this network by modularity maximisation via the Leiden algorithm,[15] which recognises clusters by the density of citation links between papers.

To describe changes over time, we constructed subgraphs that cover each decade after 1950. Each contains all OT papers published in that decade and their reference links to other OT papers. We retained any OT paper published in a previous period if it was cited in the current period. Thus, these subgraphs show citations between

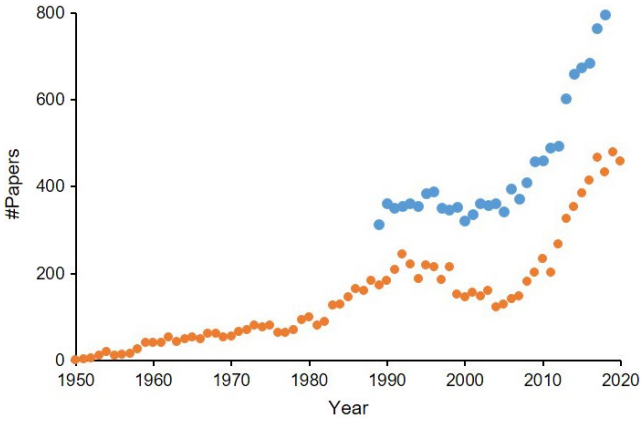

FIGURE 1 Number of papers (reviews and articles) published each year between 1950 and 2020. Orange, papers with oxytocin in the title; blue, papers with oxytocin as a topic but not in the title

OT papers in particular time periods. In the subsequent analyses, we refer to the *total citations* that a paper had accumulated as recorded in the WoS by February 2021, and the *within-network citation count* (the in-degree) – how often a paper was cited by other OT papers in the decade under analysis. To simplify interpretation, we held cluster membership constant as established by analysis of the whole network.

3 | RESULTS

3.1 | Publication and citation dynamics

Oxytocin or Pitocin were in the titles of just 27 articles published between 1928 and 1949. After 1950, the rate of publication of OT papers increases, but not at a constant rate; there is a 'bulge' between 1983 and 1992, followed by a decline to a nadir in 2004, followed by a steep increase continuing to the present day (Figure 1). After 1991, the topic search returned approximately three times as many papers as the title search; the temporal patterns were similar, but papers with oxytocin as a topic but not in the title showed less of a decline between 1992 and 2004.

Of the 10 676 OT papers, 10 357 were connected by 163 668 edges in a single weakly-connected network with an average in-degree of 15.8 – meaning that each OT paper is cited by an average of approximately 16 other OT papers. However, the average number of citations received by an OT paper (measured in the 10 years after its publication) varied with the date of publication, and we sought to understand why.

As in other fields of science,[16] most OT papers refer mainly to papers published in the previous 10 years (Figure 2B). Thus, the number of citations received by an OT paper partly depends on how many papers are published in the next 10 years that might cite it, and the number of references in those papers. The average size of reference lists increases over time[17]: OT papers in 1980-89 referred to an average of 27 papers, whereas OT papers in 2010-19 referred

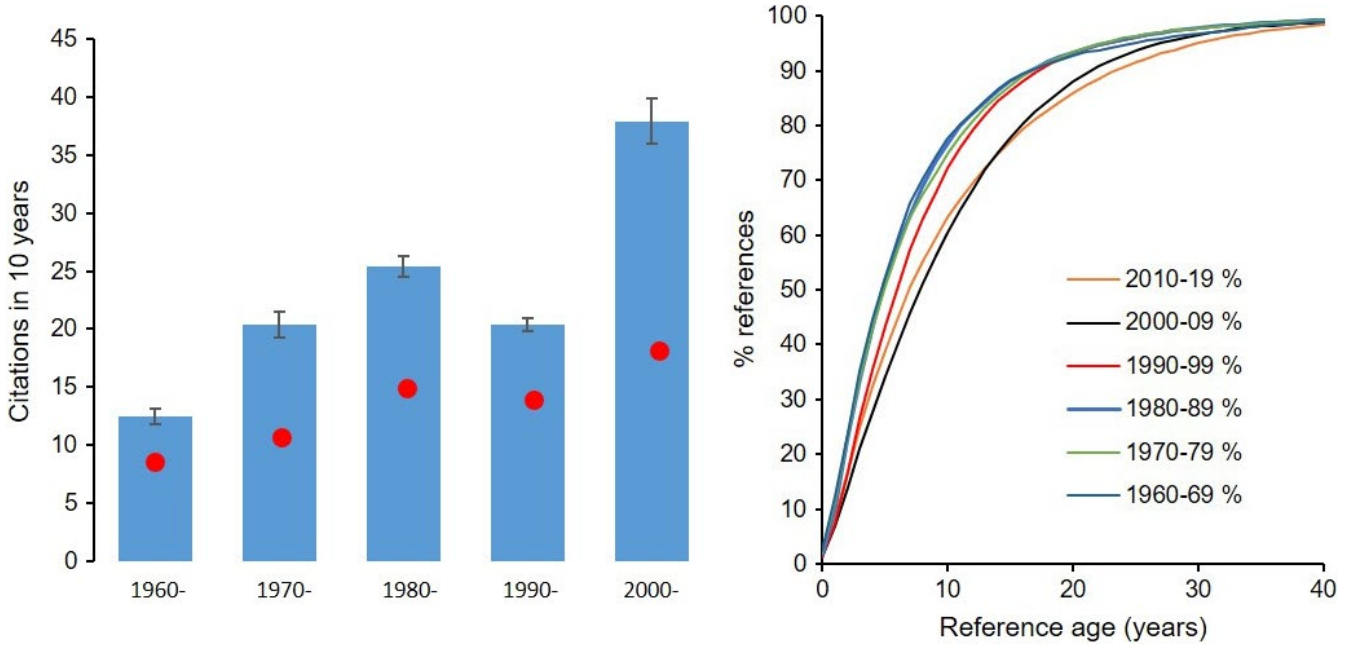

FIGURE 2 Left: mean ± SEM size of reference lists of OT papers published in each decade since 1950. The number of OT papers in each decade with reference lists that could be retrieved is given in parentheses. Note that the reference list size recorded by the Web of Science (WoS) for each paper is calculated as the number of references to other papers in the WoS Core collection. Right: age of references (years before publication of citing paper) for references cited by OT papers in each decade since 1960. Note that most references are less than 10 years old, but the average age of references has increased over time

to an average of 61 (Figure 2A). Fewer OT papers were published in 2000-2009 than in 1990-99 (1530 vs 2013), but many more were published in 2010-19 (3328). Thus OT papers published in 2000-09 are particularly highly cited (on average) (Figure 3) because of the subsequent rises in the rate of publication of OT papers (Figure 3B) and in the size of their reference lists (Figure 2A).

This is an increase in *average* citation rate: citations generally follow a heavy-tailed distribution – a relatively few papers attract disproportionately many citations (Figure 3C). This is understood to reflect 'cumulative advantage': papers with well-known authors and/or in journals with a high reputation are more likely to be noticed and cited, and papers that are frequently cited are more likely to be noticed and cited simply because they are frequently cited.[18,19] This inequality is exaggerated in OT papers published in 2000-09: the top 10% of papers published in 1990-99 received an average of 84 citations in the 10 years after publication, while the top 10% in 2000-09 received an average of 374 (Figure 3D).

3.2 | Cluster analysis

Partitioning the network identified 12 clusters, ten of which contained more than 150 papers. One comprised 53 papers on the 'oxytocin challenge test' used to diagnose fetal distress in women in labour; these studies 'used' oxytocin but are not 'about' oxytocin, and were weakly connected to other OT papers. Another comprised 62 papers on oxytocin-like peptides in invertebrates; many similar papers have the homologous peptide in the title but not oxytocin, so this cluster was poorly representative of that subfield. We removed these two clusters from the network. The ten larger clusters generally reflected communities that addressed closely-related research questions, but when papers had few citations to or from other papers, cluster membership was ill-defined. We therefore removed papers with fewer than three links to other OT papers, leaving 9648 OT papers connected by 157 853 citation links (Figure 4). Of these links, 72% (117 881) connected papers in the same cluster.

A sample of papers in each cluster was read to identify its focus. By this, we recognised the clusters to be as in the following list; the colours that we associate with each cluster are those used in Figures 4-12, and fuller statistical details are in Table 1. The order of this list follows the median date of publication of papers in each cluster from oldest to newest, and the example references given are the two papers in the cluster with the most citations from other OT papers.

(i) A 'chemistry' cluster (black) mainly reporting the development of agonists and antagonists to oxytocin.[20,21]
(ii) A 'lactation cluster' (pink), about oxytocin actions in lactation; these not only include studies on humans and on laboratory rodents, but also many on milk production in cattle and goats.[22,23]
(iii) A 'reproductive endocrinology' cluster (orange). In sheep, large amounts of oxytocin are produced by the ovaries, and this is a regulator of the ovarian cycle.[24,25]
(iv) A 'neuroscience' cluster (dark blue) focussed on the regulation of synthesis and secretion of oxytocin.[8,26]

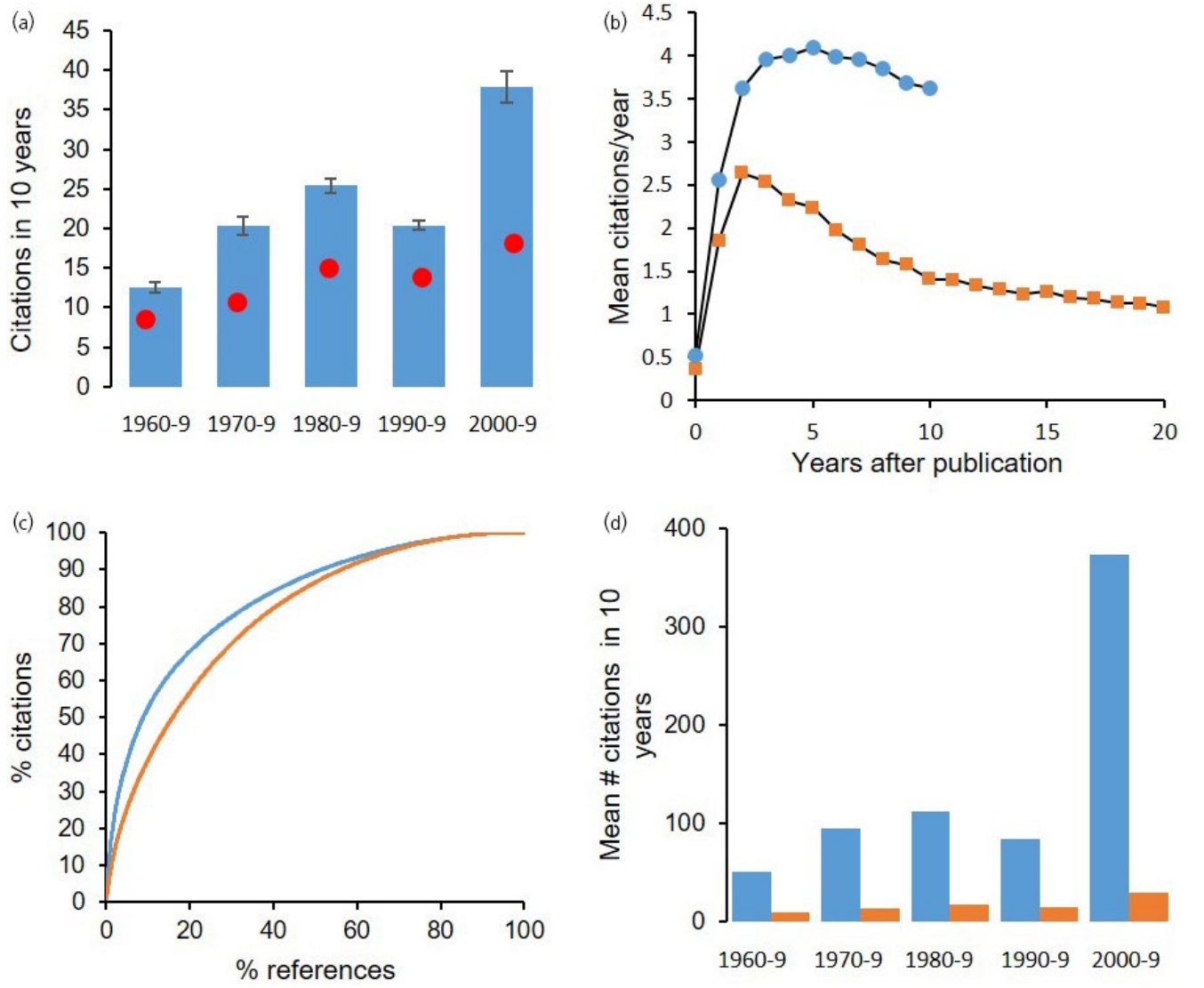

FIGURE 3 A, Mean ± SEM number of citations to oxtyocin (OT) papers published in each decade between 1960 and 2009 within 10 years of publication. The red circles show the medians. The increase in mean rate between 1990-99 and 2000-09 is more marked than the increase in medians because the increase in mean rate arises from very many citations to a relatively few papers. B, Mean citations per year after publication for OT papers published in 2000-09 (blue) and 1990-99 (orange). Mean citations are greater for papers published in 2000-09 and the decline in citation rate over the 10 years since the paper was published is slower. C, Normalised distribution of citations in the 10 years after publication for OT papers published in 2000-09 (blue) and 1990-99 (orange). Both distributions reflect the fact that a small proportion of papers attract very many citations. This feature is exaggerated in papers published in 2000-09 compared to the preceding decade. D. Mean citations received by the top 10% of papers in each decade (blue) and the remaining 90% (orange). # citations is the number received in the10 years after publication of each paper in each decade

(v) A 'receptors' cluster (green) focussed on the regulation of oxytocin receptor expression and function.[27,28]

(vi) An 'obstetrics cluster' (purple) mainly from clinicians working in departments of obstetrics and gynaecology.[29,30]

(vii) A 'behavioural neuroendocrinology' cluster (yellow) focussed on studies in animals of the effects of oxytocin on fear, stress and anxiety, and on maternal, social and affiliative behaviours.[2,31]

(viii) An 'appetite' cluster (light blue); this contains papers on oxytocin effects not only on appetite and energy balance, but also on the heart, vasculature and other peripheral tissues.[32,33]

(ix) A 'pain cluster' (dark green) comprising studies of the analgesic effects of oxytocin in the spinal cord.[34,35]

(x) A 'psychology' cluster (red) focussed on studies in humans of the psychological effects of intranasal oxytocin and its effects on brain activity, and on studies in humans that seek to associate differences in the oxytocin system with differences in social behaviour.[36,37]

4 | THE BEGINNINGS OF THE OXYTOCIN FIELD

In the 19th Century, midwives used herbal remedies to help deliver the placenta, including a fungus, *ergot*, which could stimulate the uterus

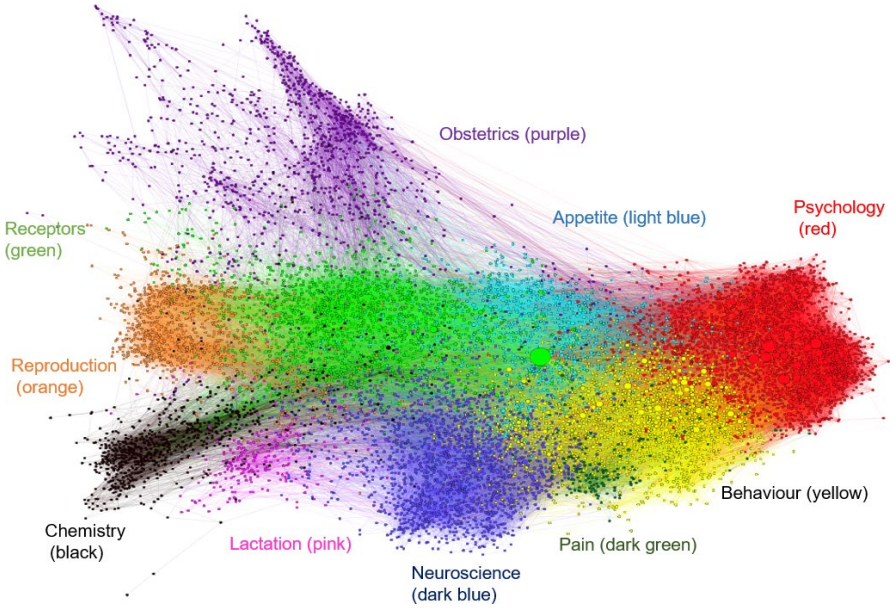

FIGURE 4 Network visualisation constructed from 9648 oxytocin (OT) papers and the 157 853 citation links between them. The nodes are coloured by cluster membership and edges between nodes are coloured by the colour of the source. The nodes are sized by in-degree (by how many citations they receive from other OT papers). The largest node (in the centre of the network and part of the green cluster) is a comprehensive review of the oxytocin receptor system.[26] To identify the clusters by topic, see Table 1

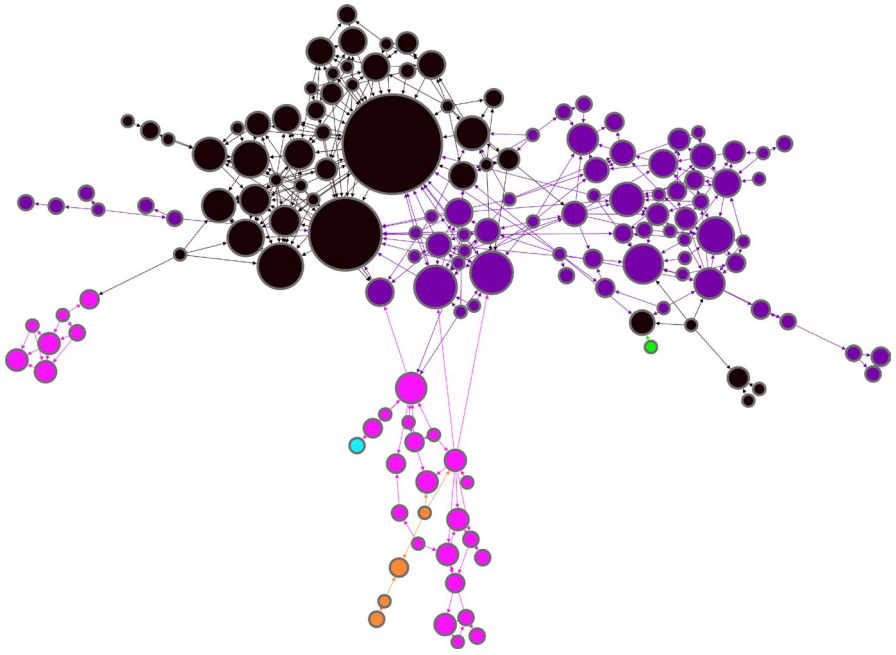

FIGURE 5 The network of oxytocin (OT) papers published before 1960. The nodes are coloured as in Figure 4. Here, 149 papers are connected by 372 citations. The largest node[19] was cited by 29 OT papers in this decade. At this level, we can see the direction of the edges – from the citing to the cited. The black nodes are 'chemistry' papers, and the purple nodes are studies of the clinical application of oxytocin – the 'obstetrics' papers. The pink nodes are 'lactation' papers: these appear as two separate groups, but they will be linked indirectly as the cluster grows in subsequent years. The green, blue and orange nodes are early representatives of other clusters that develop in subsequent decades

to contract. In 1906, Dale published a study of ergot, and, in it, he mentioned that an extract of the pituitary could also stimulate uterine contractions.[38] He interpreted this as a consequence of the 'pressor' activity of the extract – the activity that we would now attribute to vasopressin. In 1909, he published a longer account of the uterine actions, using an extract of the posterior pituitary alone.[39] That same year, Blair Bell[40] reported that, in rabbits, this extract could stimulate not only uterine contractions, but also "violent peristaltic movements" of the intestine, leading sometimes to the expulsion of faeces. *Intestinal atony* – paralysis of the intestine that produced a dangerous distension of the colon – was then a common complication of abdominal surgery, and this led Blair Bell[40] to conduct clinical studies of the extract. He noted that, when given to patients with intestinal atony, it was "unfailingly" effective in giving relief by the expulsion of intestinal gas.

Intestinal atony as a complication of surgery was virtually eliminated by advances in aseptic techniques, but the extract swiftly

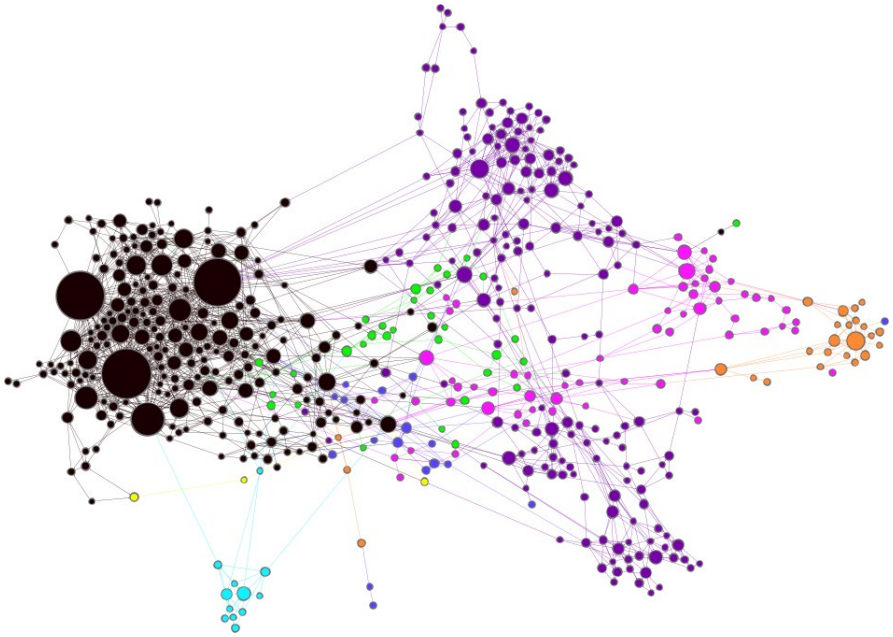

FIGURE 6 The network of oxytocin (OT) papers published in 1960-69 and all OT papers cited by these (n = 537 papers connected by 1800 citations). As in Figure 4, the nodes in black are mainly 'chemistry' papers; the nodes in purple are mainly studies of the clinical application of oxytocin (the obstetrics cluster) and those in pink are 'lactation papers', but now we see the vanguards of new clusters in orange, green, light blue and dark blue. The largest node, from du Vigneaud's group,[20] was cited 60 times by other OT papers in this decade

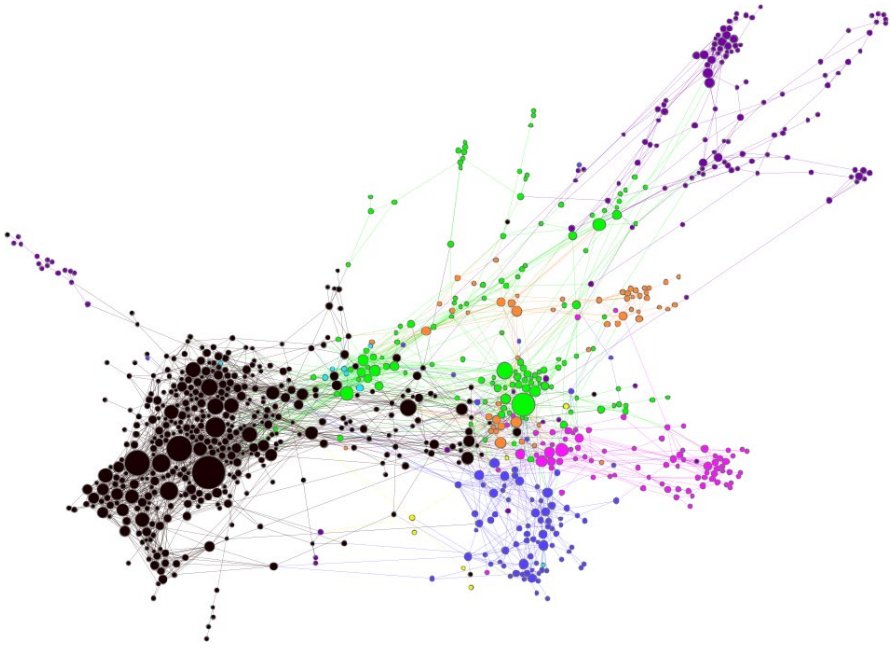

FIGURE 7 The network of oxytocin (OT) papers published in 1970-79 and all OT papers cited by these (891 papers and 3334 edges). The chemistry papers in black remain prominent, but two new clusters have grown – neuroscience papers in dark blue and receptor papers in green

entered widespread clinical use in maternity wards. This made it necessary to establish a 'standard' extract, and, in 1925, the *United States Pharmacopeia Standard Reference Powder* was adopted.[41] This was standardised by its 'oxytocic' activity – its potency at stimulating uterine contractions – as measured in 'International Units' (IU). But it also raised blood pressure, inhibited urine production and stimulated milk let-down in lactating animals. In 1928, Kamm et al[42] produced two more refined extracts: *Pitressin*, which increased blood pressure and reduced urine production; and *Pitocin*, which promoted uterine contractions and stimulated milk let-down. Kamm et al[42] hypothesised that these were each enriched in a different 'principle', which they named 'vasopressin' and 'oxytocin'. The extracts made it easier to identify the amino acid sequence of oxytocin, leading to the ability to synthesise it, advances for which du Vigneaud won the 1955 Nobel Prize in Chemistry. Thereafter, "oxytocin" was understood to be synonymous with a defined peptide, and chemically identical to a synthesised peptide that soon became important in the management of childbirth.

4.1 | The beginning of the network: Papers published before 1950

After 1928, oxytocin was understood to be not merely an extract but a *hormone*. Starling[12] had defined a hormone as a chemical messenger that is secreted from a gland and carried by the blood to act

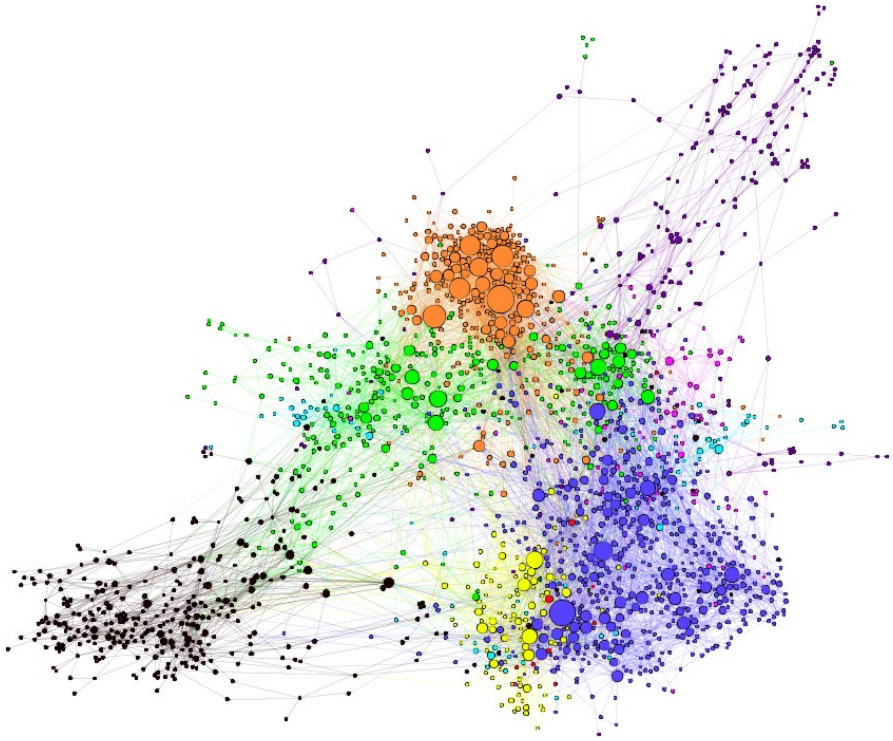

FIGURE 8 The network of oxytocin (OT) papers published in 1980-89 and all OT papers cited by these (1884 papers and 9224 edges). The largest cluster (in dark blue) comprises neuroscience papers, the most highly cited of which[25] has 85 citations within this network. The orange cluster is a tight, heavily cited set of papers on reproductive endocrinology: the most cited paper here has been cited 92 times in this decade by other OT papers.[24] The yellow papers are a new cluster on behavioural neuroendocrinology

on diverse tissues to achieve a co-ordinated response to a challenge, and he had conceived that each hormone was the agent of one physiological role. These early studies were concerned with exploring the *effects* of oxytocin; effects that might help in discerning its role, and most were concerned either with its actions on the uterus, or with distinguishing its cardiac effects from those of vasopressin. The most highly cited paper (with 73 citations) reported a lack of effect of Pitocin on the human heart.[43] The next reported that parturition is disturbed in cats when the pituitary is disconnected from the brain: it concluded that "*the work so far reported does not warrant the rejection of pituitary oxytocin as a factor involved in normal parturition*".[44] Thus, although it was taken as a "fact" that oxytocin could stimulate uterine contractions, this did not imply that parturition was controlled by oxytocin secretion. The *effect* of oxytocin on the uterus was a fact, but its *role* remained a matter of conjecture.

4.2 | 1950-59: Synthesis of oxytocin

Between 1950 and 1959, 153 OT papers were published. Of 28 that have subsequently received at least 50 citations, 17 were from chemists; 11 of these were from du Vigneaud's group, including the most highly cited OT paper published in this decade, with 945 citations to date[45] (Figure 5). These 17 papers were all members of the 'chemistry' cluster, and 59 of the 153 OT papers belong to this cluster. The other nine top-cited papers are studies of the effects of oxytocin. Four come from the 'lactation cluster', represented in this decade by 28 papers; these include studies on humans and on laboratory rodents, as well as many on milk production in cattle. Another three top papers come from the 'obstetrics cluster' with 62 papers in this decade. These include the first report of the clinical use of synthetic oxytocin, to induce labour if there was any delay and to augment its progress when progress was slow.[46] That paper, cited a total of 191 times, came from the team in Uruguay that had introduced 'Montevideo units' for measuring uterine contractions. They reported that "*… the infusion of oxytocin at the rates of 1 and 8 mU/min. respectively, increases uterine activity to values similar to those recorded at the beginning and at the end of the first stage of normal spontaneous labor; if oxytocin is the hormone controlling the contractions of the pregnant human uterus during normal spontaneous labor, a secretion rate of the same order could be predicted.*" These doses are close to those currently recommended for managing slow progress of labour in women.[47,48] A recent systematic review[49] reported that, according to the best available evidence, oxytocin levels during physiological labour are equivalent to those achieved by infusing oxytocin at 4-9 mU min^{-1}, and measured plasma concentrations of oxytocin at physiological childbirth are in the range 17-85 pg mL^{-1}, values consistent with this rate of infusion. It thus appears that these researchers, before immunoassays and indeed without *any* direct measurement of oxytocin, nevertheless accurately deduced its secretion rate during childbirth. These pioneers may not have had access to refined technologies, but they had brains and they used them.

4.3 | 1960-69: Oxytocin as a hormone

Between 1960 and 1969, 506 OT papers were published, and the top 30 have each been cited 70 times or more (Figure 6). In this decade, the chemistry cluster dominated, with 177 papers, including 17 of the top papers. The most highly cited (from Hope, Murti

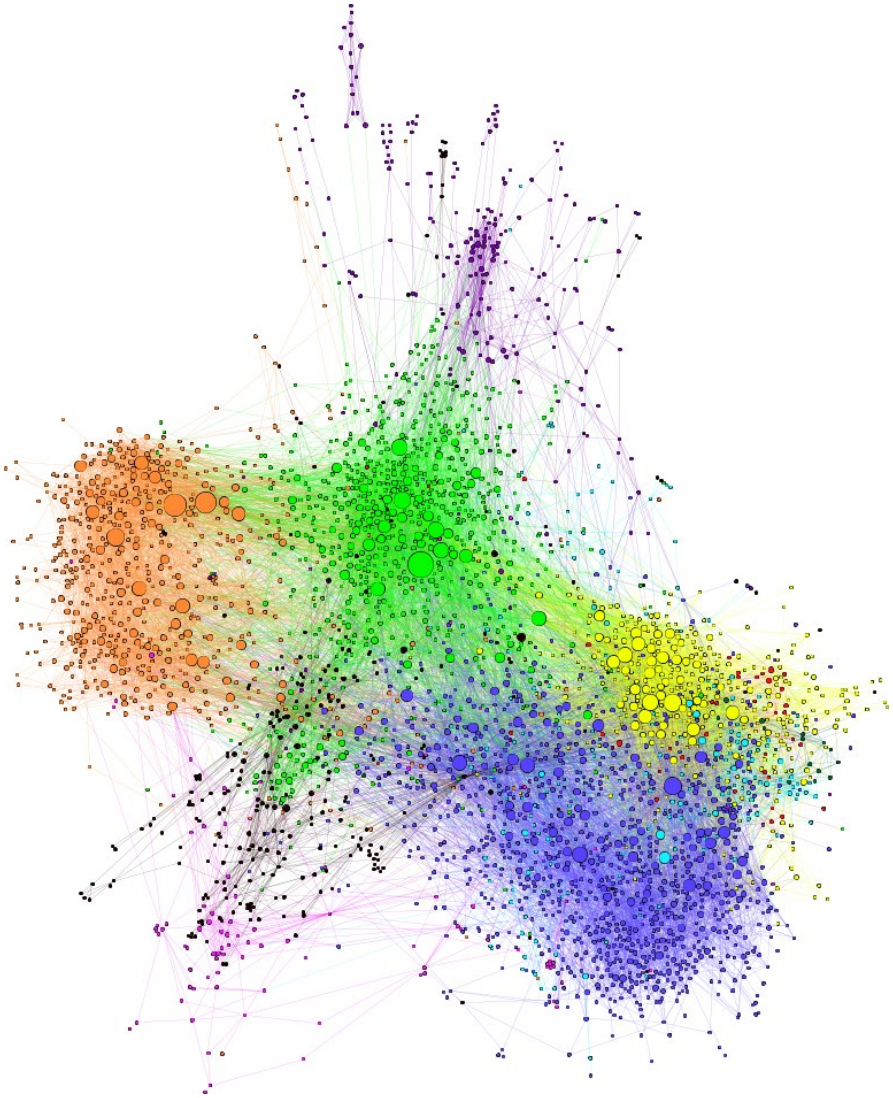

FIGURE 9 The network of oxytocin (OT) papers published in 1990-99 and all OT papers cited by these (3403 papers and 22 991 edges). The paper most cited in this decade is Kimura et al (1992) 'Structure and expression of a human oxytocin receptor'[27]; this was cited 147 times by other OT papers in this decade, and it is the largest node in the green cluster of papers on the oxytocin receptor. This is followed by Sheldrick & Flint (1985) 'Endocrine control of uterine oxytocin receptors in the ewe'[129], cited 127 times in this decade. This is the largest node in the orange cluster of papers on the endocrinology of reproduction. The orange and yellow clusters are far apart, indicating that there are few direct citation links between them. Most connectivity between clusters is mediated through the green 'receptor' cluster

and du Vigneaud) describes the synthesis of a powerful analogue of oxytocin.[21]

Darwin's notion that species arose by evolution from common ancestors implied that hormones were likely to have similar roles in different mammals, but an effect *might* occur only in some species, or only at a dose higher than any level normally achieved. Thus, oxytocin not only might have pharmacological effects that could be exploited in clinics or in controlling animal reproduction, but also, by understanding its *role*, we might recognise conditions that arise from too much or too little oxytocin. To understand what oxytocin was 'for' required *mechanistic* studies, of how and when it is produced, and of how it exerts its effects. Although the top papers include several pharmacological studies of oxytocin, including accounts of effects on the seminiferous tubule of the testis[50] and of insulin-like actions on adipose tissue,[51] others used bioassays to measure oxytocin. The most highly cited of these reported that the pituitary gland of virgin rats contained approximately 900 mU of oxytocin, whereas the content in lactating rats was approximately half of this – estimates corroborated by later immunoassays.[52] It also reported that oxytocin could be released from the isolated gland in response to depolarisation with high K^+, and that the evoked release was proportional to gland content – fundamental findings also confirmed by later studies. Other top papers included measurements of the oxytocin content of the pituitary and hypothalamus in man and other mammals.[53] Another[54] noted that "*It is still a matter of controversy whether these two peptides* [vasopressin and oxytocin] *exist within single cells as parts of a macromolecule or whether they are distinct entities in separate neurosecretory cells and available for independent release from the neurohypophysis in response to appropriate physiological stimuli*", and resolved this question by showing that electrical stimulation of different regions of the hypothalamus might release one or other of the hormones, but not always both. These three papers were in the vanguard of the 'neuroscience' cluster.

The top papers also include a report of oxytocin secretion during parturition in goats.[55] Oxytocin was found in the blood of only one of eight goats studied during the first stage of labour, but "was present in appreciable quantities" during the second stage, rising to a maximum when the head presented. Thus it was questioned whether oxytocin played *any* role in the initiation of labour, and it was unclear whether the reported increase in secretion during parturition was a

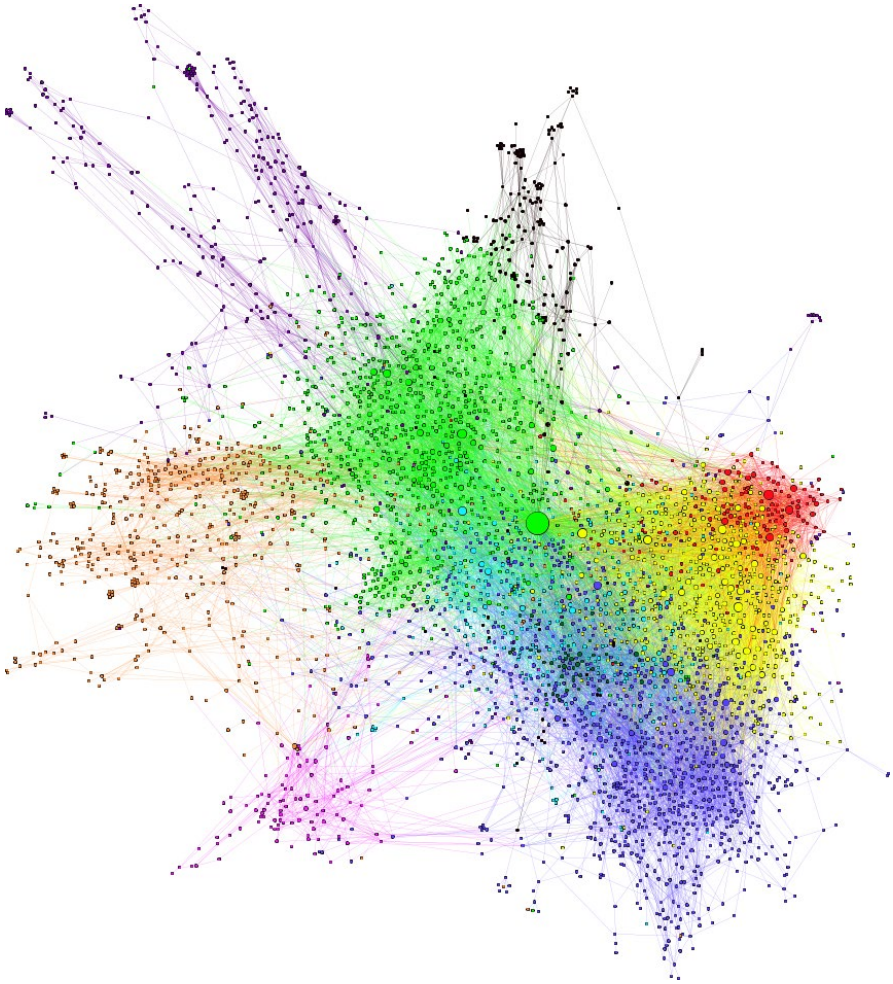

FIGURE 10 The oxytocin network as constructed from oxytocin (OT) papers published in 2000-09 and all OT papers cited by these. The network has 3932 nodes (papers) and 21 624 edges. The paper most cited within this network is a review of oxytocin receptor physiology[27], cited 264 times, within the receptor cluster (green), The next is Kosfeld et al (2005)[36], cited 94 times in a new cluster, in red, that is dominated by papers using intranasal administration of oxytocin. The next is Nishimori et al (1996)[88], cited 86 times in the 'behavioural' cluster' (yellow)

cause of foetal expulsion or a *consequence* of it, arising from vaginal and cervical distension. If the latter, what was the physiological role (if any) of oxytocin during parturition? Theobald[56] led the attack on muddled thinking; for him, the extreme sensitivity of the uterus to oxytocin at term implied that labour was probably initiated by concentrations of oxytocin too low to measure reliably, while the very high levels reported at delivery were probably mismeasurements due to interfering factors in plasma: in his words, "*It is the uncritical acceptance of frequent and expansive estimates of blood oxytocin, and the conjectures based on them, which have led some obstetricians astray. On the one hand some have come to doubt whether oxytocin plays any part in parturition, while on the other it has become fashionable to use monumental doses of oxytocin, to deliver them by routes which defy absorption analysis, and to accept consequent rupture of the uterus as an acceptable risk.*" Theobald was targeting the use of intranasal oxytocin, then commonly given at the 'monumental' dose of 5 IU at intervals of 15 minutes to assist labour.[57]

4.4 | 1970-79: Immunoassays and immunohistochemistry

In this decade, 769 OT papers were published, and 33 of these had been cited more than 150 times by 2021 (Figure 7). The chemistry cluster contributed 230 OT papers; only five of these are among the top papers, but the paper most highly cited within this decade is again the 1962 paper from Hope et al,[21] cited by 59 OT papers in the decade.

The ability to synthesise oxytocin had led to the ability to produce antibodies to it, and this gave rise to two technologies that enabled studies to move beyond pharmacology. Eight top papers used *immunocytochemistry* to "see" oxytocin in neurones. The most cited paper (by total citation count) of the decade reported that, although most oxytocin neurones project to the pituitary, some project to other sites in the brain.[26] Oxytocin, it was inferred, is a "neuropeptide", released not only into the blood, but also into the brain. Another six top papers reported electrophysiological studies: the most highly cited (with 293 citations) defined how the oxytocin neurones behave during suckling,[58] and another (272 citations) revealed their responsiveness to the Na^+ content of the blood.[59] These are among 72 papers from the 'neuroscience' cluster; 16 of the top papers are among them.

Another four top papers used *radioimmunoassays*. These were no more sensitive than the bioassays used previously, but hundreds of samples could be assayed at a time. The most highly cited of these reported measurements of oxytocin in cerebrospinal fluid (CSF), interpreted as evidence that oxytocin is indeed released within the brain.[60]

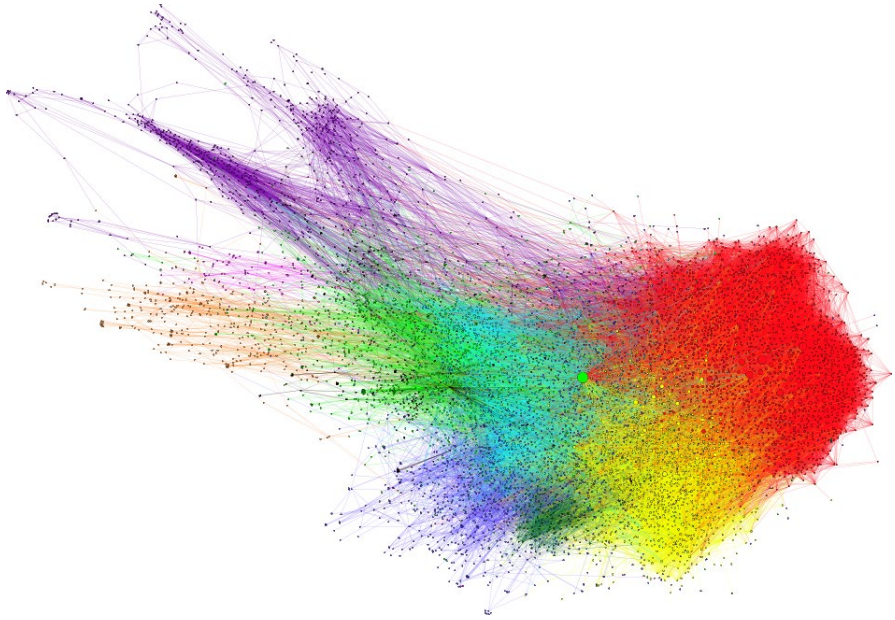

FIGURE 11 The oxytocin network as constructed from oxytocin (OT) papers published in 2010-20 and all OT papers cited by these (7420 nodes (papers) and 98 440 edges). The paper most cited within this network is Gimpl & Fahrenholz (2001)[27], cited 905 times (the large green node in the centre of the network). The red cluster is now massive, and includes many papers using intranasal oxytocin in humans but also studies measuring plasma oxytocin in humans in connection with psychological indicators, and studies of oxytocin pathway genes in populations classified by psychological indicators. The dark green cluster at the bottom of the network, between the neuroscience cluster in blue and the behavioural neuroendocrinology cluster in yellow, is a new cluster on pain. The light blue cluster is the appetite cluster

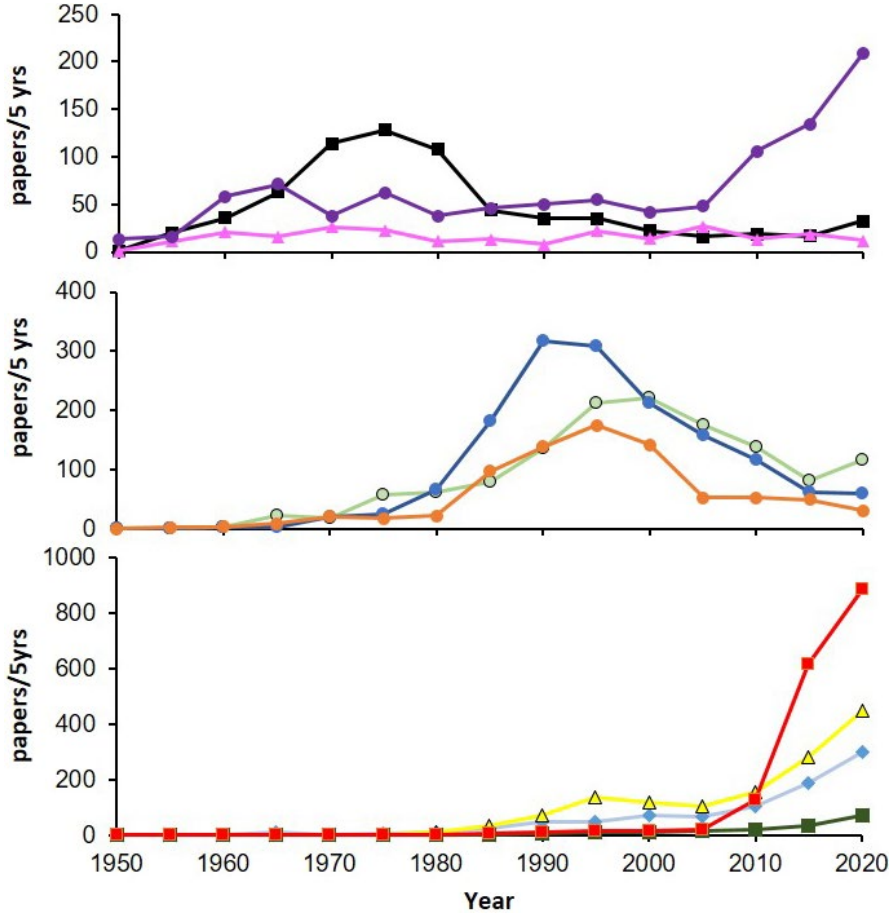

FIGURE 12 Evolution of the clusters between 1950 and 2020. Each line traces the number of papers in a cluster published in each 5-year interval. The lines are colour coded to be consistent with the colouring in Figure 11. Before 1970, most papers belong to the chemistry cluster (black) the obstetrics cluster (purple), or the lactation cluster (pink). Between 1980 and 2010, the field is dominated by papers in the neuroscience cluster (dark blue), the receptor cluster (light green) and reproductive endocrinology (orange); since 2010, the field has seen the rise of the psychology cluster (red) and the behavioural neuroscience cluster (yellow), but also sharp increases in the appetite cluster (light blue) and a new pain cluster (dark green) – and a rise in obstetrics papers

TABLE 1 Details of the clusters shown in Figure 4, giving the mean size of reference lists of papers within each cluster, the mean number of citations to those papers, and the proporion of references/citations that are to:from other OT papers in the network

				References		Citations	
Cluster	Colour	Age (median)	Papers	Mean	% to network	Mean	% from network
Chemistry	Black	1975	690	30.0	27	28.8	31
Lactation	Pink	1984	237	23.5	26	21.5	29
Reproduction	Orange	1993	808	33.2	35	29.9	41
Neuroscience	Dark blue	1993	1528	40.1	26	41.3	31
Receptors	Green	1997	1322	34.7	36	32.7	44
Obstetrics	Purple	2001	985	22.5	28	18.0	34
Behaviour	Yellow	2012	1355	63.2	40	53.7	48
Appetite	Light blue	2012	868	47.5	39	28.7	51
Pain	Dark green	2015	159	51.9	40	27.1	57
Psychology	Red	2016	1691	44.8	45	49.0	56

Just two top papers were concerned with effects on the uterus. A new focus of attention was the *oxytocin receptor*: oxytocin was now established to be secreted during parturition and in response to suckling in experimental animals, although its effects depend on the level of expression of receptors in the uterus and mammary gland. However, in women, it proved hard to find *any* increase in oxytocin secretion during parturition: the massive increase in receptor expression in the uterus is decisive in stimulating the uterine contractions that deliver the baby, not any large change in secretion.[61] Of the OT papers published in this decade, 109 belong to the 'receptor cluster'.

Three top papers reported surprising effects of oxytocin on the brain, and became the vanguard of a 'behavioural neuroendocrinology' cluster. Two reported on 'amnesic' effects of oxytocin; these were associated with the theory that vasopressin enhances certain forms of memory, a theory that encountered intense criticism in the 1980s and was largely abandoned.[62] The third reported effects of oxytocin on maternal behaviour. Virgin or pregnant rats pay little attention to pups placed in their cage, but, after she has given birth, a mother rat will build a nest into which she will gather not only her own pups, but also any strange pups that are introduced into the cage. This behaviour, it was now reported, can be triggered in virgin rats by injecting oxytocin into the brain[63] *if* the rats have first been 'primed' by injections of oestrogen.

4.5 | 1980-89: Agonists, antagonists and receptors

In this decade, 1423 OT papers were published, 40 of which had been cited more than 200 times by 2021 (Figure 8). The development of potent, selective agonists had enabled oxytocin receptors to be localised to particular cells, as well as their abundance to be measured. This led to two influential findings. First, oxytocin receptors are present not only on the uterine myometrium, where they directly affect contractility, but also on decidual tissues where they regulate prostaglandin secretion; because prostaglandins can also evoke uterine contractions, this is a part of the mechanism by which oxytocin acts.[64] Indeed, recent studies in transgenic mice deficient in oxytocin receptors and/or prostaglandin F2α receptors appear to have confirmed that both are important for successful parturition.[65] Second, the increasing responsiveness of the uterus to oxytocin in late pregnancy is dictated by the regulation of oxytocin receptor expression.[66] Of the OT papers published in this decade, 205 belong to the receptor cluster.

Other top papers[25,67] addressed the finding that, in sheep, large amounts of oxytocin are produced by the ovaries[68] and that this is a regulator of the ovarian cycle. These belong to the cluster of papers on reproductive endocrinology, 204 of which were published in this decade.

This decade also saw the publication of 463 "neuroscience" papers. The structure of the oxytocin gene was now revealed,[10] and a new technique, in situ hybridisation, enabled oxytocin mRNA to be measured in individual cells. This was used in one top paper to show that, in the rat, the levels of oxytocin mRNA are markedly increased not only during lactation, but also in response to salt intake.[69] Other top papers included studies of the projections of oxytocin neurones[70] and of oxytocin receptor distribution in the brain. Oxytocin receptors were often found at sites that receive no oxytocin-containing nerve fibres,[71] and this raised questions about whether oxytocin is indeed a neurotransmitter. Conventionally, a neurotransmitter is a substance released at synapses between neurones, whereas a hormone is released into the blood and acts at distant targets. Neither definition meets the circumstance that oxytocin may be released at some sites within the brain yet acts at other, relatively distant sites, nor the circumstance that oxytocin secreted from the dendrites of oxytocin neurones could facilitate its own release.[72] The decade also saw the collapse of the illusion that each neurone uses just one messenger to communicate with other neurones: oxytocin neurones co-express and co-secrete many biologically active peptides,[73] although mostly in relatively tiny amounts. Some of these appear to have physiological roles,[74] but many may be mere biological 'noise.'

The most cited OT paper of the decade[75] (and three other top papers in the behavioural cluster) followed up the report that oxytocin can stimulate maternal behaviour. Attempts to replicate these experiments in rats were not consistently successful,[76-79] but after it was reported that oxytocin can also induce maternal behaviour in sheep,[80] the issue appears to be settled. Another top paper reported that oxytocin is involved in regulating prolactin secretion in response to suckling,[81] an effect apparently harmonious with its role in milk-ejection; it remains controversial whether this is a physiological effect or a purely pharmacological effect.

Other top papers reported that oxytocin is secreted in response to food intake[32]; that its actions in the brain affect appetite[33]; that it is released in response to certain types of stress[82]; that it is secreted by men and women during orgasm[83]; that it can facilitate sexual behaviour in female rats[84]; and that in the rat it acts on the kidneys to promote sodium excretion.[85] How were *these* diverse actions compatible with the role of oxytocin in regulating parturition, lactation, and maternal behaviour? Although it might have been imagined that there was not one oxytocin system in the brain but many, that notion has gained little support. Almost all of the oxytocin in the brain is produced by neurones that project to the posterior pituitary.[86,87]

4.6 | 1990-99: The neuropeptide

Between 1990 and 1999, 2033 OT papers were published; these have subsequently been cited approximately 78 000 times, and 38 of them had been cited more than 200 times by 2021 (Figure 9). It was now clear that oxytocin had many physiological roles, but was not be essential for all of them. Two top papers showed that, although oxytocin 'knockout' mice cannot feed their young, they appeared to give birth normally and showed normal maternal behaviour.[88,89] In rodents, oxytocin appeared to be important for electrolyte homeostasis: its production and secretion are markedly increased in response to salt intake, and it promotes sodium secretion through direct actions on the kidneys and through stimulation of atrial natriuretic peptide secretion from the heart.[90] One of the top papers of the 1990s reported that, in rats, oxytocin has this effect at the low concentrations present in the circulation (5-6 pg mL^{-1}), implying that this is a physiologically relevant action[91] – but, as had been shown by a 1986 paper, high sodium levels do not increase oxytocin secretion in man.[92]

Most attention turned to the central actions of oxytocin. These were addressed by a series of highly cited reviews, each with a distinctive focus. One focussed on the diversity of central actions of oxytocin, including on feeding, cardiovascular regulation and thermoregulation[93]; another on its effects on sexual behaviour, penile erection and lordosis[94]; another made the case for the essential role of centrally released oxytocin in the milk-ejection reflex[8]; and another argued that central release of oxytocin is regulated independently of peripheral secretion, and involves secretion from dendrites by a mechanism very different from synaptic release of neurotransmitters.[6]

Three papers published in this decade have each been cited more than 500 times: the first is a review proposing that oxytocin mediated 'the benefits of positive social interactions and emotions' through diverse central and peripheral actions, including by lowering blood pressure, alleviating pain, reducing cortisol secretion and raising insulin levels.[95] The second reported the structure and expression of the human oxytocin receptor.[28] The third,[96] following a report that i.c.v. oxytocin could facilitate the formation of partner bonds in monogamous prairie voles,[97] argued that differences in social behaviour between different vole species reflected differences in the distribution of oxytocin receptors. These studies, inspired originally by the finding that oxytocin can promote maternal behaviour, now led to the notion that oxytocin might be involved in social behaviour in man – and might lead to a therapy for autism.[98] Another highly-cited paper (481 citations) reported that, in a small sample, autistic children generally have low plasma concentrations of oxytocin[99]; subsequent larger studies have not consistently replicated this.[100]

The fourth most highly cited study of this decade reported that central administration of oxytocin to rats at a very low dose (1-10 ng h^{-1} administered continuously i.c.v. by an osmotic minipump) markedly attenuated stress-induced secretion of corticosterone, and reduced anxiety as measured by behaviour on an elevated plus maze.[101] This study became key evidence for the case, amply developed in subsequent studies, that oxytocin, released in the brain in response to stressors, has an important role in alleviating anxiety.[2]

4.7 | 2000-09: Intranasal oxytocin

In this decade, 1533 OT papers were published, with more than 80 000 citations by 2021 (Figure 10). As in every decade from 1960, approximately one-third of the papers received approximately 75% of the citations (Figure 3C). The most highly cited paper (with > 2000 citations) reported effects of intranasal oxytocin on how human subjects play a "trust game"[36] with monetary stakes where success requires the player to develop trust in a playing partner. This game, first described in 1995, was an established part of the repertoire of *behavioural economics*. Intranasal application of oxytocin was not new; in the 1960s, it was widely used for the induction and augmentation of labour[57] before being abandoned in favour of the much more reliable intravenous delivery. The trust study used a dose of 24 IU, close to the total pituitary content of oxytocin in man, and more than twice the amount needed to facilitate childbirth. This paper inspired the idea that autism and other social behaviour disorders might be treatable by a simple, minimally invasive intervention.

The second most highly cited OT paper[27] is a review of oxytocin receptors, emphasising their widespread expression in peripheral tissues including the kidney, heart, thymus, pancreas and adipocytes, and the diverse actions of oxytocin at these sites and in the brain. Its focus is the regulation of these receptors by gonadal and adrenal steroids – a striking feature still poorly understood. This paper is part of the 'receptor cluster', but it is also highly cited by all the other clusters.

Thirty-six papers published in this decade had been cited at least 300 times by 2021, including 13 studies of intranasal oxytocin. Another four of the top papers are studies of genetic variation in the oxytocin receptor, suggesting associations with autism,[102] parenting behaviour[103] and stress reactivity[104]; these all belong to a new cluster of 'psychology' papers. Eight are reports of studies in rodents, all linked to behavioural actions of oxytocin. These include two reports of social deficits in transgenic mice that lack oxytocin receptors[105,106]; these mice cannot distinguish between mice they have met before and unfamiliar mice. These papers are part of the 'behavioural neuroendocrinology' cluster that mainly comprises experimental studies on laboratory rodents involving interventions in oxytocin pathways in the brain, and their consequences for various behaviours.

The highest cited paper in the obstetrics cluster remains the 1957 study mentioned above,[46] although two papers published in 2000-09 have each been cited more than 150 times; both concern not the uterotonic effects of oxytocin but its haemodynamic effects.[30,107] Women undergoing caesarean section are often given oxytocin at a high dose (5 IU i.v.) to reduce bleeding after delivery, an effect mediated by V1 vasopressin receptors. However, the effects include tachycardia, hypotension and decreased cardiac output; these pose risks for some patients, and it is important to minimise them.

4.8 | 2010-19: The social peptide

Between 2010 and 2019, 3752 OT papers were published, with almost 100 000 citations (Figure 11). Two have received more than 900 citations; these are both reviews of the 'social effects' of oxytocin in humans.[37,108]

Several hundred articles were studies using intranasal oxytocin in humans. One is the only study to date that has tried to measure how much intranasally administered oxytocin reaches the brain in humans.[109] It used the dose of 24 IU (a dose that had become standard for these studies) and collected CSF from patients by lumbar puncture. Four patients were sampled after 45 minutes and another four after 60 minutes. This is the period in which psychological effects have been assessed, but the oxytocin levels at these times were no different from those in patients given a vehicle control. Another three patients were sampled at 75 minutes, and these showed modestly elevated levels. This study is widely cited (277 times to date) as confirmation that intranasal oxytocin enters the brain.

Although there is now a huge volume of studies using intranasal oxytocin, there is also scepticism, expressed in several highly-cited reviews. In 2015, a meta-analysis of studies on oxytocin and trust concluded that "*the cumulative evidence does not provide robust convergent evidence that human trust is reliably associated with [oxytocin] (or caused by it)*".[110] Another review argued that "*intranasal OT studies are generally underpowered and that there is a high probability that most of the published intranasal OT findings do not represent true effects*".[111] A third argued that "*very little of the huge amounts applied intranasally appears to reach the cerebrospinal fluid. However, peripheral concentrations are increased to supraphysiologic levels, with likely effects on diverse targets including the gastrointestinal tract, heart, and reproductive tract*".[112] Finally, a fourth pointed to evidence of a 'file-drawer effect' in which negative studies were left unpublished.[113] Most recently, a systematic review of the effects of intranasal oxytocin on psychosocial outcomes concluded that "*(a) tested interactive IN-OT effects were highly heterogeneous; (b) for most published interactions, no replication was attempted; (c) when attempted, replications were largely unsuccessful.*"[114] Such concerns have led to calls for adequately powered and pre-registered replication studies of the most commonly reported effects of intranasal oxytocin. In 2020, *'A registered replication study on oxytocin and trust'*, published in *Nature Human Behaviour*[115] reported a failure to replicate the findings of the pivotal, massively cited study of Kosfeld et al.[36]

Many studies in this decade pursued a mechanistic understanding of the involvement of oxytocin in social behaviours through studies in rodents. The most highly cited of these, with more than 500 citations, reported that optogenetic activation of oxytocin release in the amygdala could attenuate a conditioned fear response in rats.[116] Few rodent studies involved the use of intranasal oxytocin, but three that did have each been cited more than 100 times: one reported that chronic intranasal oxytocin caused long-term impairments in bonding behaviour of prairie voles[117]; another reported that chronic intranasal oxytocin caused long-term impairments in social behaviour in mice[118]; and a third reported that intranasal administration of oxytocin in rats produced no significant change in CSF oxytocin, but raised oxytocin concentrations in some brain areas. This study measured oxytocin in brain samples collected using intracranial microdialysis – a technical approach that inevitably disrupts the blood-brain barrier at the probe location.[119]

This decade also saw growing interest in the effects of oxytocin on appetite, energy expenditure and body composition, and six primary research papers on this theme have each been cited more than 100 times.[120-124] These are part of an 'appetite cluster' that also contains papers on oxytocin effects on the heart, vasculature and other peripheral tissues.

Eleven highly cited papers address the analgesic effects of oxytocin – the neurones in the spinal cord that carry pain messages from the periphery are innervated by oxytocin neurones, and there is interest in the idea that this might be exploited by new treatments for pain relief.[125] These are part of a 'pain' cluster, comprising 159 papers. The first papers in this cluster appeared in the 1980s, but 72 papers – approximately half of the cluster – were published between 2015 and the end of 2020.

In this decade, the notion that the behavioural effects of oxytocin might be mediated by the parvocellular neurones of the PVN, whereas magnocellular neurones were solely concerned with the peripheral effects of oxytocin, appears to have collapsed. The population of oxytocin neurones that project centrally but not to the posterior pituitary now appears to be quite tiny, comprising mostly neurones that project to the caudal brainstem and to the spinal cord, and a small amount that mediate communication between the paraventricular and supraoptic nuclei. On the other hand, not only do

the magnocellular neurones release very large amounts of oxytocin within the hypothalamus from their dendrites, but also many of them project to the posterior pituitary, as well as diverse sites in the forebrain. The neuronal targets include neuronal populations linked to appetite, including sodium appetite, thermogenesis, pain, stress, fear, and social and sexual behaviour. The oxytocin neurones appear to be mainly a single population, but one that is multifunctional and multisensory. These are properties that have also been inferred (by comparative genomics) to be features of a remote ancestor of modern magnocellular neurones – neurones that, in the last common ancestor of all bilateral animals, a marine mollusc that lived 450 million years ago, expressed a peptide homologous to oxytocin.[126]

Oxytocin has been part of the normal management of childbirth for more than 70 years, and although other clusters have come and gone, there has been a steady stream of papers reporting the results of clinical trials of oxytocin in labour wards, addressing indications and contraindications for its use, and comparing it with alternative medications. In the decade 2000-09, 132 OT papers were published in this obstetrics cluster. By contrast, between 2010 and 2020, 369 OT papers were added, including a review of oxytocin actions on post-partum haemorrhage that has already gathered 125 citations.[127] In 2018, a paper in *The New England Journal of Medicine*[128] compared oxytocin with carbetocin, a long-acting oxytocin agonist. Oxytocin, the current standard therapy for preventing postpartum haemorrhage, must be stored between 2°C and 8°C. The trial found that carbetocin was as effective as oxytocin in preventing postpartum haemorrhage, but, because it can be produced in a way that makes it heat stable, its use incurs lower transport and storage costs and less waste, and it can be used in many more settings worldwide. Of the papers in the obstetrics cluster published since 2010, 36 have 'carbetocin' in the title as well as oxytocin.

5 | EVOLUTION OF THE FIELD

By this analysis, we have 'parsed' the oxytocin field, as represented by approximately 10 000 OT papers published over more than 70 years, into just ten major 'clusters' (Figure 12). In each of these clusters, a high proportion of their references are to other OT papers – and mostly to papers in the same cluster. Similarly, a high proportion of the citations to them originate from the same cluster. For example, the largest cluster, the 'psychology cluster', gets approximately 56% of its citations from other OT papers, and 81% of these are from the psychology cluster, whereas 45% of its references are to other OT papers and 77% of these are to papers in the psychology cluster. Thus each cluster represents a very densely interconnected body of papers (Table 1).

The 'chemistry' cluster is defined by both discipline and a clear research objective – to define the structural features that determine how molecules will bind to the oxytocin receptor, and to use this knowledge to generate potent and selective agonists and antagonists with good bioavailability. The objective can be phrased in this way only with hindsight – at the height of activity in this cluster, it was not clear whether there were one or several oxytocin receptors or how selective they might be. By 1985, well before the sequencing of the oxytocin receptor, activity in this cluster was declining – it had apparently achieved its major goals. As activity in the chemistry cluster declined, three new clusters rose – the neuroscience cluster, the receptor cluster and the reproductive endocrinology cluster (Figure 12).

By the end of 2020, the reproductive endocrinology cluster contained 808 papers that had been cited more than 24 000 times. This is an average of approximatety 30 citations per paper, but, of the 114 papers published since 2006, only one (with 31 citations) has reached this average. The most highly cited paper, with 323 citations, was published in 1976; it reported that oxytocin could simulate prostaglandin secretion from the endometrium of the uterus in sheep.[24] Most of the papers are studies in sheep or cattle. Many continued to address the role of oxytocin in stimulating prostaglandin secretion from the endometrium, but about half focused on the production of oxytocin by the corpus luteum,[25] the stimulation of oxytocin secretion from the corpus luteum by prostaglandins,[67] and its role in luteolysis.[129] Thus this cluster has a focus on specific questions – what does oxytocin *do* in the ovary, and how are prostaglandins involved in this? Oxytocin receptors are present in the ovaries of many mammals, but cattle and sheep are unusual in that oxytocin is also produced in abundance there. The cluster reached a peak in 1980-89: of the 47 papers with at least 100 citations, 28 were published in this decade. Its rise followed the emergence of radioimmunoassays that made it possible to reliably measure oxytocin in frequent blood samples and to measure tissue content. But, by approximately 2000, it appeared that the will to pursue these questions was evaporating, either because they had been adequately answered, or because they had not led to new questions of perceived importance, or perhaps because the main drivers of the cluster had retired. Probably all three were true in part; to outsiders, the story of ovarian oxytocin seemed elegant and convincing, but it appeared to be a cul-de-sac, in being specific to certain species with no clear relevance to humans.

The rise of the neuroscience cluster can also be related to the emergence of new techniques. The availability of antibodies, first produced for radioimmunoassays, led to the development of immunohistochemistry, enabling the oxytocin neurones and their projections to be visualised. Advances in molecular biology led to the application of in situ hybridisation for studying oxytocin mRNA expression; and, in electrophysiological studies, the application of antidromic identification made it feasible to monitor the electrical activity of single, identified magnocellular neurones in living animals in real time.[5] These developments enabled the oxytocin neurones to be studied at a level of detail without precedent in neuroscience. They were instrumental in what, in retrospect, might be seen as an extended research programme to establish the biochemical, anatomical, electrophysiological and functional phenotype of the oxytocin neurone.

Between 1970 and 2000, the chemistry, neuroscience and reproductive endocrinology clusters are separate, but are linked via the receptor cluster. This cluster appeared to choose this name for itself; of the 1322 papers that it contains, 17 have been cited at least

TABLE 2 Total number of citations to papers in each cluster from OT papers in the network, shown by the cluster of origin of those citations. In each cluster, most citations come from papers in the same cluster

Cluster	Psychology	Behaviour	Obstetrics	Neuroscience	Reproduction	Appetite	Pain	Lactation	Chemistry	Receptors
Psychology	37 758	912	199	895	74	1022	238	25	64	7786
Behaviour	286	12 183	271	878	1017	394	42	63	648	820
Obstetrics	168	517	4994	84	27	87	8	20	88	157
Neuroscience	138	820	75	12 405	370	541	60	117	157	1188
Reproduction	8	857	25	309	7980	18	1	68	48	52
Appetite	1753	1291	183	1316	78	9192	161	49	105	2027
Pain	476	197	18	262	8	192	1629	1	13	512
Lactation	11	46	18	123	86	34	0	1057	35	25
Chemistry	66	311	73	39	14	26	10	21	4836	72
Receptors	5595	1598	89	3184	153	1273	317	27	150	22 139

200 times, and 'oxytocin receptor' is in the title of 14 of these. This cluster captured some papers from chemists that we might have expected to find in the chemistry cluster, but, for the most part, it is about the biochemical and physiological consequences of oxytocin binding to its receptor in different tissues, and how receptor expression is regulated. Because these are important to many other clusters, this cluster is more 'extrovert' than any other, in having more references to other clusters and in receiving more citations from other clusters (Table 2).

The psychology cluster has little overlap with any of the disciplines prominent in other clusters; it includes papers from psychiatrists, psychologists and neurologists that investigate the effects of intranasal oxytocin, studies looking for genetic markers that might reveal links between oxytocin pathways and social behaviour, and studies relating concentrations of oxytocin in plasma, urine or saliva to social behaviour. It includes some critical reviews from scientists whose research papers are in other clusters, but it contains few papers from animal studies, except some that have addressed the bonds between dogs or their owners. Its papers report the effects of oxytocin, but have little in common with the pharmacological studies in other clusters; dose-response studies are effectively absent, and there is little concern about specificity or selectivity – there are almost no controls using related peptides, and no studies using selective agonists or antagonists. The chemistry cluster had, by the end of the 1980s, produced many selective and potent agonists and antagonists – an armamentarium exploited in every other cluster in the oxytocin field, but not by the psychology cluster. It appears that the psychology cluster is 'in' the oxytocin field, yet not 'of' it.

Noting the conspicuous representation of papers on autism and schizophrenia, it appears that this cluster is driven by an important question – can we use intranasal oxytocin to treat conditions of social impairment? It is this question that makes the psychological studies salient, as they seem to define the scope of the therapeutic potential of oxytocin. The *mechanisms* by which the effects arise seem of secondary relevance – it is as though it does not matter *how* it works, it is enough to know *that* it works – or it will be enough if we can find a relevant effect that is robustly replicable.

However, rapid growth it is not limited to the psychology cluster. We have already mentioned the acceleration in the publication of papers in the obstetrics cluster; the pain cluster may be the smallest at present but it is the fastest growing, and the 'appetite' cluster, after a long period of slow growth between 1960 and 2010, now also appears to be growing rapidly. Neither the pain cluster, nor the appetite cluster, nor the obstetrics cluster have much connection with the psychology cluster or with each other – their growth appears to be the consequence of factors specific to each cluster.

6 | REFLECTIONS

The output of science, as measured by the number of papers published, has been growing exponentially for more than 100 years, with a doubling time of about 10 years. This growth shows no sign

of slowing. Increasingly, scientists must rely on reviews and meta-analyses to maintain an awareness of even quite narrow research fields. Meta-analyses are becoming increasingly rigorous, but are really only applicable to questions where the aggregation of results from similar studies is possible. In some areas, systematic reviews are becoming common, where a literature survey is led by a systematic search strategy. However, it is difficult to determine whether a search strategy has captured the relevant literature exhaustively, or even captured a representative part of it, and if the interpretations embedded in that literature depend on a separate body of literature, that critical feature may be missed entirely. For example, a systematic search of the literature on intranasal oxytocin and social behaviour is likely to miss the older literature on intranasal oxytocin in the management of parturition and lactation, and hence miss the demonstration of peripheral actions of the applied oxytocin at doses far lower than used in recent psychology studies.[112] Such a search is also likely to miss the older literature on oxytocin measurements where issues of sample matrix interference with immunoassays were recognised.[41]

Systematic searches and meta-analyses ideally require objective measures of study quality, but the diversity of study designs and methods involved in research on many questions makes this unrealistic. Here, we have attempted to describe the development of a field objectively – or at least in a transparent way that is reproducible. We have used citation counts not as a measurement of quality (for which they are wholly unfitted), but as a measure of academic influence. In the Supporting information, we list all of the papers in this data set together with their cluster membership and key bibliometric data.

This analysis throws a spotlight on the structural features of science that ensure a massive inequality in how papers are cited. In every subfield and in every decade, there are 'winners' of this citation game; these tell of the flows of fashion, opportunity and excitement, and that is enough for us without our needing to reflect on the quality of the papers that we refer to.

We have seldom mentioned the authors of papers. Every highly-cited OT paper rests on many other OT papers, and most are highly cited mainly because they are cited by many other OT papers. A paper can become highly cited only when the time is ripe for it to be so – when there is an active and growing community receptive to the claims that it makes. The notion that a high citation count is an index of a paper's *quality* seems lazy, absurd, and pointless, but we can use the highly cited papers to help identify what research questions are pertinent to different research communities at different times.

It has been commonly assumed that referencing should attempt to recognise priority, should sometimes imply quality, and should recognise the senior authors by name, at least when they are well known. Here, we have (for the most part) named authors only when we have felt the need to quote from them, intending to write about the ideas more than about the authors, and hoping to avoid any appearance of either patronage or obsequiousness. In making the case that these ideas are socially constructed, we mean that they are less the product of individual idiosyncrasy or brilliance, than of diverse interactions, both supportive and argumentative, between many authors.

Ideas have become prominent in the literature through a mixture of pressures on citing authors, including the pressures to maximise academic impact (by publishing in areas that gain many citations) and socio-economic impact (by publishing on topics that appear to have translational potential). Paradoxically, the pressure to publish on 'hot topics' seems destined to eventually produce papers that, on average, are unusually poorly cited. When a subfield, such as that represented by the psychology cluster, grows rapidly, the number of potentially citable papers will soon greatly exceed the number of citation opportunities afforded by reference lists. At this point, reference selection becomes increasingly constrained by the perceived need to cite established 'totems', giving less space to cite more than a few of the abundant new papers.

No less paradoxically, papers with an actual practical impact (as distinct from papers that claim a potential practical impact) are seldom highly cited, and this is apparent in the two clusters overtly concerned with translating fundamental research into practical application – the obstetrics cluster and the lactation cluster. Oxytocin has comprised one of the most important hormones ever discovered for the part that it has played in reducing the mortality of women in childbirth, a role extended and refined by systematic clinical studies guided by our understanding of oxytocin receptor physiology, and by the development and pharmacological characterisation of agonists such as carbetocin, as well as antagonists developed to prevent pre-term labour. But such studies, being often concerned more with the quantification of risks and benefits than with the understanding of causes, are more *answers* than *questions*. They often need few references and, in speaking to practitioners more than to researchers, they often receive few citations.

To be true to our own conclusions in this paper, we must be indifferent to whether it will be cited, but we hope it will be read. We have seen messages in this story of oxytocin. The older literature may be technically limited, but its authors were not short of wit and intelligence, and they had a sophisticated understanding of the methods and apparatus available to them. Sometimes those methods were superior to those now in common use. In the 1980s, many laboratories specialised in the development of highly sensitive radioimmmunoassays for oxytocin, and invested time and care in sample preparation techniques to ensure their analytical validity; we now see a collapse of confidence in measurements of oxytocin with the emergence of commercial assays that are used without appropriate sample preparation.[41] The insights from earlier workers can easily be forgotten, and may remain hidden from a new generation for whom history may seem irrelevant.

We hope that *this* OT paper will be a map to treasures buried in the older literature, as well as a reminder of not only our debts to our predecessors, but also our dependence on the community of which each author is just a small part. A paper can make an impact only because of the existence of a community that it can impact upon, a community that can refine, correct, dispute, extend or embellish its

content, and the impact of any paper is the success of that community, not of the authors alone. Our understanding of oxytocin, as of anything in science, is inevitably path-dependent: which ideas take root and flourish is a consequence of not only their brilliance, but also their timeliness – the fortuity of their emergence at what can be seen in retrospect as an auspicious time.

ACKNOWLEDGEMENTS

This work was supported by the Economic and Social Research Council (ESRC) Postdoctoral Fellowship Scheme (URL: https://gtr.ukri.org/projects?ref=ES%2FV011790%2F1). The funder had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

AUTHOR CONTRIBUTIONS

Gareth Leng: Conceptualisation; Formal analysis; Project administration; Writing – original draft; Writing – review & editing. **Rhodri I. Leng:** Conceptualisation; Formal analysis; Investigation; Methodology; Visualisation; Writing – original draft; Writing – review & editing.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/jne.13014.

ORCID

Gareth Leng https://orcid.org/0000-0002-2388-8466

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Leng G, Leng RI. Oxytocin: A citation network analysis of 10 000 papers. *J Neuroendocrinol*. 2021;33:e13014. https://doi.org/10.1111/jne.13014