Systematic Review

A Scientometric Approach to Review the Role of the Medial Preoptic Area (MPOA) in Parental Behavior

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Abstract: Research investigating the neural substrates underpinning parental behaviour has recently gained momentum. Particularly, the hypothalamic medial preoptic area (MPOA) has been identified as a crucial region for parenting and other parent-related behaviour. The current study conducted a scientometric analysis of publications from 01 January 1972 to 19 January 2021 using CiteSpace software to determine trends in the scientific literature exploring the relationship between MPOA and parental behaviour. 677 scientific papers were analysed, producing a network of 1,509 nodes and 5,498 links. Four major clusters were identified: "C-Fos Expression", "Lactating Rat", "Medial Preoptic Area Interaction" and "Parental Behavior". Their content suggests an initial trend in which the properties of the MPOA in response to parental behavior were studied, followed by a growing attention towards the presence of a brain network, including the reward circuits, regulating such behavior. Furthermore, while attention was initially directed uniquely to maternal behavior, it has recently been extended to the understanding of paternal behaviors as well. Finally, although the majority of the studies were conducted on rodents, recent publications broaden the implications of previous documents to human parental behavior, giving insight into the mechanisms underlying postpartum depression. Potential directions in future works were also discussed.

Keywords: Medial Preoptic Area; MPOA; Parental behavior; Scientometry; Systematic Review; CiteSpace; Document Co-Citation Analysis; Keyword Analysis

Citation: Carollo, A.; Balagtas, J.P.M.; Neoh, M.J.Y.; Esposito, G. A Scientometric Approach to Review the Role of the Medial Preoptic Area (MPOA) in Parental Behavior. *Preprints* **2021**, *1*, 0. https://doi.org/

1. Introduction

Across many species, social encounters and interactions are ubiquitous and the regulation of social behaviours is essential for health and survival. With the advent of neurobiological methods, researchers are able to investigate the neural basis underlying social behaviour, gaining insight into processes of the brain that govern social behaviour. Among the wide range of social behaviours, this paper will focus on the study of parental behaviour and its neurobiological basis.

As young in mammalian species are usually altricial at birth, parental care is often a critical aspect for the survival and development of offspring. Parental behaviours form a complex category of activities influenced by a range of internal and external factors [1], where laboratory rodents are popular animal models used to study these factors. In rodents, general responses can be categorized into nurturance, indifference/avoidance and infanticide. Specifically, parental behaviours include active behaviours such as nest construction, pup retrieval and licking of pups and (ii) quiescent behaviours such as quiescent positioning over pups (see Lonstein and Fleming [2]). Sex differences are observed in parenting behaviours where male and female rodents differ in spontaneity of parental behaviours. While both virgin and postpartum female mice are spontaneously maternal and have an innate motivation to care for their pups [2,3], virgin males often engage in infanticide where they attack and kill newborn pups as an adaptive reproductive strategy to increase their mating opportunities [4–7]. On the other hand, male mice only become parental in the weeks following mating [8]. Similarly, female rats are (i) less likely to be infanticidal

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[7,9,10], (ii) more spontaneously responsive to pups or likely to become parentally sensitized [11–13] and (iii) more consistent in displaying particular parental behaviours [14,15].

In terms of the neurobiology underlying parental behaviours in rodents, the medial preoptic area (MPOA) of the hypothalamus – an area involved in thermoregulation and sexual behaviour – is one of the key areas which has been implicated and is often considered a central node in the control of parenting. Empirical studies found (i) lesions in the MPOA disrupted parental behaviour [16], (ii) high expression of receptors of modulators of parenting such as estrogen, oxytocin, progesterone and prolactin [17], (iii) facilitation of parental behaviour when the MPOA is directly stimulated with estrogen [18,19]. Levels of galanin, a neuropeptide, has also been found to govern parental behaviour in mice. Loss of galanin neurons in the MPOA was associated with a reduction in parental behaviour in male and female mice while optogenetic activation of galanin neurons reduced pup-directed aggression and induced active pup grooming in male mice [8].

2. The Present Study

Considerable progress in identifying brain areas and neural mechanisms underlying parenting has been made in the last few decades (see [20,21] for reviews). Given the size of the body of this work, the present study used a scientometrics approach to investigate influential and impactful publications in this field through document co-citation analysis (DCA; eg. [22]), where a co-citation is defined as the citation of two sources together in the same paper. The DCA will show clusters of co-citing publications and papers and temporal and structural metrics of these clusters will be discussed. Specifically, we aim to investigate: (i) common topics of the clusters of publications co-citing each other and (ii) impactful publications. In order to accomplish the first aim, an analysis of keywords and indexing terms will support the DCA. The results of the scientometric approach will provide greater insight into research trends and publications in the field of the neurobiology of parenting behaviour.

3. Materials and Methods

For the present study, the sample of publications was downloaded from the database on Scopus, as done in previous scientometric publications [23,24]. A total of 677 scientific works, published between 01 January 1972 to 19 January 2021, was obtained by using the following research string for the search: “(TITLE-ABS-KEY (“medial preoptic") OR TITLE-ABS-KEY (“MPOA") AND TITLE-ABS-KEY (parent*) OR TITLE-ABS-KEY (matern*) OR TITLE-ABS-KEY (patern*) OR TITLE-ABS-KEY (mother*) OR TITLE-ABS-KEY (attach*) OR TITLE-ABS-KEY (nurtur*) OR TITLE-ABS-KEY (offspring) OR TITLE-ABS-KEY (pup*) OR TITLE-ABS-KEY (attack*) OR TITLE-ABS-KEY (infanticid*) OR TITLE-ABS-KEY (“young")) AND (LIMIT-TO(LANGUAGE, “English"))". After downloading the dataset of publications, scientometric analysis was conducted via CiteSpace software (version 5.7.R3). Data was imported in CiteSpace and 43,669 of the 43,728 (99.0%) total references cited in the collected papers were considered valid. The amount of invalid references can be consider as irrelevant [25].

To examine the connections between scientific works investigating the relationship between medial preoptic area and parenting, a DCA was first conducted. DCA is a type of analysis based on the frequency in which two documents have been co-cited (cited together) by subsequent works [26]. In the analysis, the g-index selection criteria was adopted with scale factor k set at 25. The selection criteria and the value for its scale factor were chosen after several trials in which we aimed to optimize the metrics of the network. In particular, we attempted the analysis with g-index with k set at 25 and 15, TOP N with N at 50, 15 and 10 and TOP N% with N at 10. The DCA was subsequently supported by a keyword analysis and the same optimization of node selection criteria was conducted. In this case, the best selection criteria turned out to be TOP N with N fixed at 10.

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Structural metrics were used to examine the overall configuration of the network and the details of each node. Structural metrics include modularity Q, silhouette score and betweenness centrality. Modularity Q is an index that ranges from 0 to 1 and indicates the extent to which a network is divisible into single modules or clusters [27]. The homogeneity of these modules is measured using the silhouette score, with values ranging from -1 to 1. The higher the value of silhouette score, the higher the consistency of nodes among the module [28,29]. Betweenness centrality applies to single nodes to describe the degree in which a single node functions as a bridge to connect other nodes which would otherwise be separate. Centrality values range from 0 to 1, where high scores close to 1 indicates likely groundbreaking ideas [24]. For the analysis of single nodes, alongside the already mentioned structural metrics, temporal metrics were examined as well. This group of metrics mainly refers to citation burstness and sigma. Citation burstness is an index of the citation burst strength for each node which indicates an abrupt change in the frequency in which a node has been cited within a period of time [30]. Theoretically, values of citation burstness can range from 0 to infinite. Sigma is a metric obtained by considering betweenness centrality and citation burstness at the same time. Sigma values are computed following the equation $(\text{centrality}+1)^{burstness}$ [28], and they indicate the novelty and the influence of a node among the network of interest.

4. Results

4.1. Document Co-Citation Analysis

The network we obtained for the DCA was composed of 1,509 nodes and 5,498 links (see Figure 1. This means that, on average, each node in the network was connected with 3.64 other references. Furthermore, the network showed a modularity Q index of 0.3841 and a weighted mean silhouette of 0.9257. Thus, the nodes form a network which is modestly divisible into separate modules, each of which is highly homogeneous.

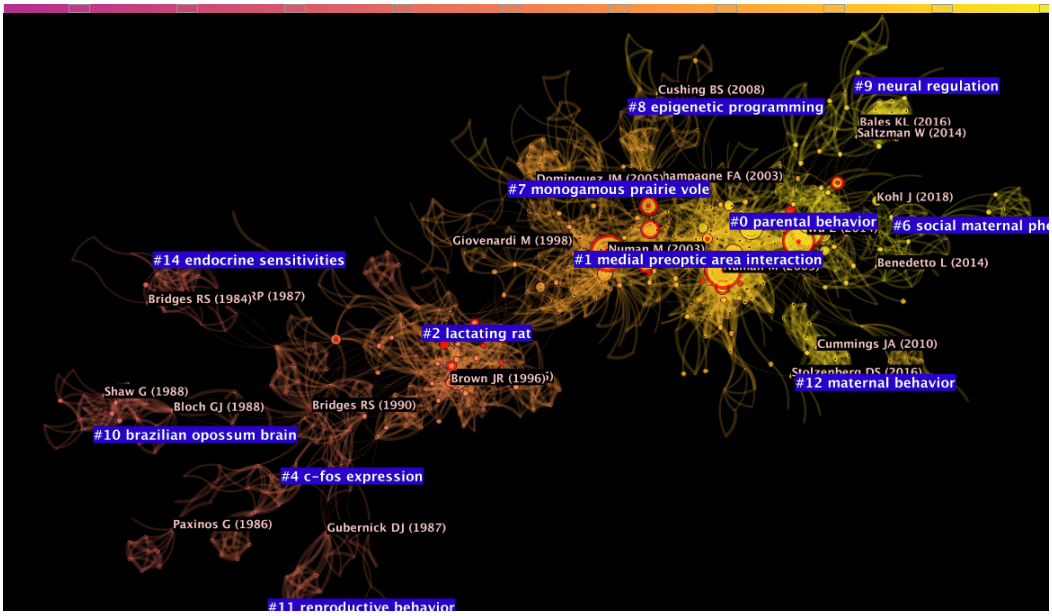

Figure 1. Network of publications generated through the Document Co-Citation Analysis (DCA) using CiteSpace. Nodes belonging to the 17 major clusters among the network are displayed.

The major clusters identified in the DCA were highly internally homogeneous (see Figure 2 and Table 1). The largest cluster, cluster #0, that was identified consisted of 190 nodes, had a silhouette score of 0.879 and the references composing it were, on average, published in 2010. Cluster #1 was a group of 129 nodes with a high silhouette score of 0.885 and a publication year that, on average, was 2002. The third largest cluster, that is cluster

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#2, was a group of 115 nodes with a high silhouette score of 0.902 and were on average, published in 1994. The next cluster, cluster #4, consisted of 69 nodes, had silhouette of 0.915 and mean publication year of 1990. Considering the average year of publication of the documents forming a cluster, cluster #6 was the most recent one (mean year of publication = 2014; size = 50; silhouette = 0.968) together with cluster #9 (mean year of publication = 2014; size = 36; silhouette = 0.99).

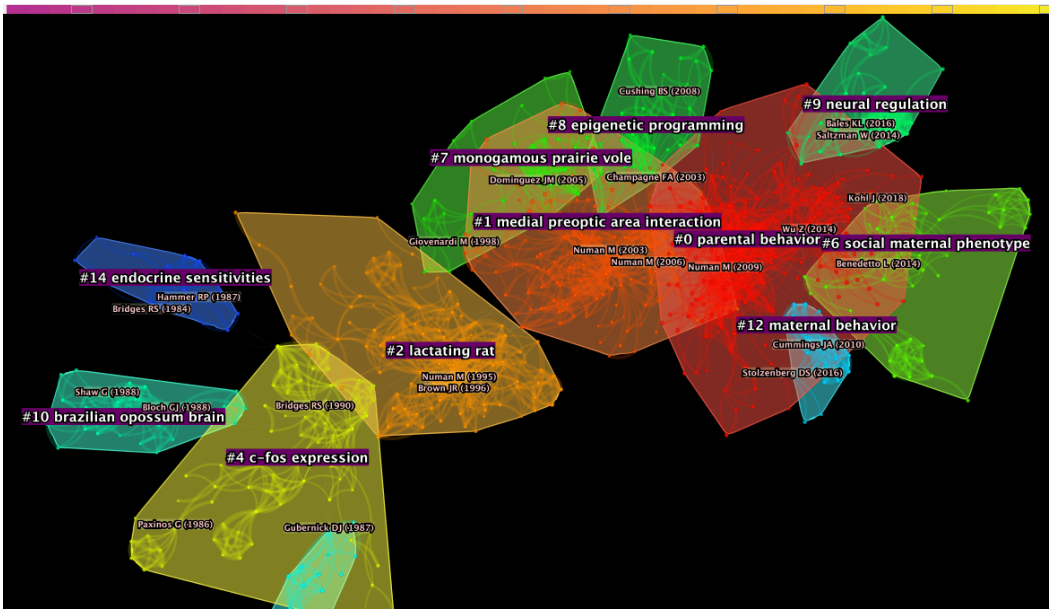

Figure 2. Network of publications generated through the Document Co-Citation Analysis (DCA). The 17 major clusters are highlighted and divided by colour.

Table 1. Metrics of the 10 largest clusters identified by computing the Document Co-Citation Analysis (DCA). In the table, Cluster ID, Size of the cluster, Silhouette of the cluster and Mean Year of publications are reported.

Cluster ID	Size	Silhouette	Mean Year
0	190	0.879	2010
1	129	0.885	2002
2	115	0.902	1994
4	69	0.915	1990
6	50	0.968	2014
7	41	0.966	2001
8	39	0.983	2004
9	36	0.99	2014
10	29	0.989	1987
11	27	0.983	1987

In the network, 55 nodes showed a citation burst in their history (see Table 2 for the 20 nodes with the highest value of citation burstness). In particular, among the 10 nodes with the highest magnitude of citation burstness, 6 belonged to cluster #0, 3 to cluster #1 and 1 to cluster #2. Specifically, among the three documents with the strongest magnitude of citation burst, 1 belonged to cluster #1 and 2 to cluster #0. In order of burst strength, these three references were authored by Numan and Insel [17], Wu *et al.* [8] and Numan and Stolzenberg [31]. The document authored by Numan and Insel [17] showed a citation burst of 18.61, which started in 2005, two years after its publication. Wu *et al.* [8] were the authors of the publication with the second highest citation burst in the network, with a

 doi:10.20944/preprints202102.0612.v1

value of 16.05 and a duration of 5 years. Finally, the third document with the strongest citation burst, specifically 14.55, was authored by Numan and Stolzenberg [31]. Among the 20 references reported in Table 2, M. Numan was the first author for 7 of the references. Among these, the node by Numan *et al.* [32] had the longest citation burst in the network, with a duration of 8 years (from 2005 to 2013). As for the sigma metric, the document with the highest value was again the one published by Numan and Insel [17], with a value of 3.02. Other references with high sigma values were authored by Numan and Stolzenberg [31] and Champagne *et al.* [33], with sigma values of 2.29 and 1.91 respectively.

Table 2. Sample of the 20 publications with high citation burstness metrics generated in the DCA. Alongside the strength of citation burstness for a document, the table reports the document's year of publication, the beginning and the end of the burst in citations and its duration. Values for sigma and centrality metrics are also reported.

Reference	Strenght of burstness	Year	Beginning of burstness	End of burstness	Burst duration	Sigma	Centrality
Numan and Insel [17]	18.61	2003	2005	2011	6	3.02	0.06
Wu *et al.* [8]	16.05	2014	2015	2020	5	1.84	0.04
Numan and Stolzenberg [31]	14.55	2009	2010	2017	7	2.29	0.06
Tsuneoka *et al.* [34]	13.67	2013	2014	2020	6	1.49	0.03
Numan [35]	10.95	2006	2007	2013	6	1.71	0.05
Numan and Numan [36]	10.24	1995	1997	2002	5	1.16	0.01
Dulac *et al.* [37]	9.58	2014	2015	2020	5	1.19	0.02
Shahrokh *et al.* [38]	8.94	2010	2011	2017	6	1.48	0.04
Pereira and Morrell [39]	8.90	2011	2013	2020	7	1.29	0.03
Numan *et al.* [32]	8.26	2005	2005	2013	8	1.58	0.06
Bridges [40]	7.39	2015	2016	2020	4	1.00	0.00
Stack *et al.* [41]	7.20	2002	2005	2010	5	1.28	0.04
Bosch and Neumann [42]	7.19	2012	2013	2020	7	1.11	0.01
Champagne *et al.* [33]	7.09	2004	2005	2012	7	1.91	0.10
Brown *et al.* [43]	6.99	1996	1997	2002	5	1.41	0.05
Keer and Stern [44]	6.59	1999	2004	2007	3	1.18	0.03
Numan and Numan [45]	6.30	1994	1998	2002	4	1.21	0.03
Numan [46]	5.92	2007	2008	2015	7	1.05	0.01
Meddle *et al.* [47]	5.83	2007	2010	2014	4	1.01	0.00
Tsuneoka *et al.* [48]	5.82	2015	2017	2020	3	1.01	0.00

4.2. Keywords Analysis

The Keywords Analysis produced a network of 55 nodes and 161 links, meaning that each identified keyword was connected with 2.93 other ones. Furthermore, the resulting network showed a modularity Q index of 0.2488 and a weighted mean silhouette of 0.7898. In the network, 22 nodes showed a citation burst (see Table 3). In particular, by looking at the strength of their citation burst, *support*, *metabolism* and *physiology* had the highest magnitudes of 49.07, 42.12 and 33.13, respectively. *Support* is a keyword used especially as an indexing term in the Medical Subject Headings (MeSH) database, and it refers to the funding of the research. As for the duration of the citation burst, two keywords were particularly relevant: *rat* (Strength of burstness = 7.15; Burst duration = 22 years) and *hypothalamus* (Strength of burstness = 24.34; Burst duration = 21 years). *Hypothalamus* was also the keyword with the earliest beginning of citation burst, which started in 1972. The other references with the earliest beginning of burstness were *theoretical study* (Beginning of burstness = 1974) and *rat* (Beginning of burstness = 1977). Conversely, the keywords with a more recent citation burst were *metabolism* (Beginning of burstness = 2015), *physiology* (Beginning of burstness = 2015), *maternal behavior* (Beginning of burstness = 2016) and *male* (Beginning of burstness = 2018).

 doi:10.20944/preprints202102.0612.v1

Table 3. Twenty-two (N = 22) keywords with the generated citation burstness metric in the Keywords Analysis. Alongside the strength of citation burstness for a keyword, the table reports the year of beginning and end of the burst in citations for a keyword and its duration in time.

Reference	Strength of burstness	Beginning of burstness	End of burstness	Burst duration
support	49.07	1979	1995	16
metabolism	42.12	2015	2020	5
physiology	33.13	2015	2020	5
central nervous system	28.94	1978	1987	9
hypothalamus	24.34	1972	1993	21
medial preoptic area	14.02	2010	2020	10
maternal behavior	11.07	2016	2018	2
pregnancy	10.05	1978	1985	7
male	8.59	2018	2020	2
protein expression	7.90	2002	2010	8
preoptic area	7.82	2004	2008	4
rat	7.15	1977	1999	22
estradiol	6.55	1987	1989	2
radioisotope	6.54	1984	1990	6
animal tissue	5.57	2009	2011	2
endocrine system	5.37	1982	1984	2
ovariectomy	5.24	1987	1989	2
theoretical study	4.82	1974	1977	3
histology	4.67	1980	1982	2
aging	4.55	1978	1989	12
brain	4.24	1987	1988	1
animal cell	3.92	1987	1989	2

5. Discussion

5.1. Document Co-Citation Analysis

The content of the major clusters, whose titles were given using the Log-Likelihood Ratio (LLR) option, identified through the DCA is discussed below chronologically.

5.1.1. Cluster #4: “C-Fos Expression"

In Table 4, the most active citing documents for cluster #4 are reported. c-Fos is an immediate early response gene encoding a transcription factor that is part of the AP-1 transcription factor complex, which is involved in the regulation of cell proliferation. c-Fos has also been found to be a marker of neuronal activity (see [49]). In particular, as the name of the cluster suggests, some references in the cluster focused on understanding the underlying mechanisms of parental behavior by examining Fos-like immunoreactivity (Fos-lir) in the brain. This approach allowed researchers to find that MPOA is a crucial area for the onset and maintenance of parental behavior. In fact, the MPOA has a greater number of cells showing Fos-lir in maternally active rats [50–52]. Within this cluster, the onset of maternal behavior in rats was also examined in relation to lactogen and the central administration of human placental lactogen. Specifically, the work by Bridges and Freemark [53] and Bridges *et al.* [54] showed that human placental lactogen infusion in the MPOA of steroid-primed nulliparous rats facilitates the onset of maternal behaviors towards a foster young, similar to what was reported for prolactin [55–58]. For this reason, some references in which authors explored the functional and structural properties of the response to prolactin were included in cluster #4 [59–64]. The role of estrogens has also been studied by part of the references of this cluster in regards to maternal behavior in rodents [65–67]. For instance, the study by Rosenblatt *et al.* [68] showed that the MPOA is crucial for maternal behavior even in male rats and that such behavior benefits from a prolonged estradiol and progesterone treatment. This interest found in the citing documents justifies the presence of papers studying the localization and distribution of estrogen receptors in various animals’ brains, such as rodents [69] and quails [70] within the cluster. The study of estrogens and the MPOA, occasionally with a focus on aromatase action, permitted researchers to explore the sexual dimorphism reported for this brain area as well [71–77].

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Table 4. All the 9 citing documents in cluster #4 identified using the DCA.

Cluster	Citing Document	GCS	Coverage
4	Nagano and Shinoda [78]	20	9
4	Bridges *et al.* [54]	78	9
4	Fleming and Walsh [51]	79	9
4	Fleming and Korsmit [52]	108	8
4	Dellovade *et al.* [77]	32	7
4	Rizvi *et al.* [79]	135	7
4	Rosenblatt *et al.* [68]	75	6
4	Bridges and Freemark [53]	34	6
4	Ehret and Buckenmaier [67]	36	5

5.1.2. Cluster #2: "Lactating Rat"

In Table 5, the most active citing documents for cluster #2 are reported. As the name of the cluster suggests, part of the references in this group studied the relationship between MPOA and parental behavior by focusing on lactating rats. For this reason, some works within the cluster are cited because they explore the brain response to prolactin, the levels of which increase during lactation [80–87]. Other hormones related to this phase have been studied as well [88–90]. For instance, the increased binding of oxytocin in MPOA at parturition seems to be important for the molecule to stimulate the postpartum activation of maternal behavior [91]. This onset of maternal behavior after parturition depends on lateral habenula neurons [92–94,94]. As observed in the previous cluster, the MPOA is a brain area that shows an increase in the immediate early gene c-fos or other Fos proteins in maternally active rats [45,51,52,95–100]. Such activation of the MPOA appears to have a causal role for the ability to nurture young animals [43,68]. Thus, references composing cluster #2 aimed to better understand some properties of such responses [101–105]. For instance, Lin *et al.* [106] showed that FosB and Fos in the MPOA (and other areas) are involved in the neural activation during parturition and lactation, not in pregnancy, in rats. Also, a part of that neural activation seems to be independent from olfactory and other sensory inputs, indicating the presence of efferent neurons crucial for the performance of maternal behavior [36,107]. Furthermore, Lonstein and De Vries [108] reported that many of the neurons showing c-fos activity after maternal behavior are involved with the synthesis of the inhibitory neurotransmitter GABA. For this reason, the authors concluded that some neurons in the MPOA, especially in its dorsal part, must have either a local or diffuse inhibitory effect as a component of maternal behavior. These results were also detected for other brain areas, such as the ventral bed nucleus of the stria terminalis and the caudal ventrolateral periaqueductal gray. Knowledge of the presence of a circuit of inhibiting maternal behavior within the hypothalamus and in connected brain regions started to emerge from studies of the beginning of 2000s [109,110]. In the same years, Komisaruk *et al.* [111] reported that in parturient and hysterectomized rats, there is an increase in excitatory interactions in the MPOA. By examining Fos expression during maternal behavior, Stack *et al.* [41] observed that the MPOA likely modulates the activity of two brain regions: the shell of the nucleus accumbens, and the intermediate part of the Lateral Septum. Another work by Lonstein *et al.* [112] documented that a number of Fos-immunoreactive (Fos-ir) neurons also express the alpha subtype of the estrogen receptor (ERα), suggesting that postpartum maternal behavior could be influenced by ERα activity [18]. In fact, [113] noted that MPOA's susceptibility towards the effects of estrogen increases right after pregnancy termination. To highlight the connection between estrogens and Fos-ir neurons in MPOA, c-fos expression inducted in rodents' brain by estradiol administration has been reported in the literature [114,115]. In fact, evidence of the central role that such hormones have on maternal behavior comes from studies on the administration of estrogen-progesterone treatment (to simulate a pregnancy-like pattern of hormonal environment) to nonpregnant

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and ovariectomized rats. These animals were still able to manifest maternal behaviours with treatments simulating the hormonal pattern of pregnancy [116].

Table 5. Major 10 citing documents in cluster #2 identified using the DCA.

Cluster	Citing Document	GCS	Coverage
2	Kalinichev *et al.* [100]	54	21
2	Stack *et al.* [41]	103	15
2	Lonstein *et al.* [112]	72	14
2	Komisaruk *et al.* [111]	31	13
2	Sheehan and Numan [113]	48	13
2	Stack and Numan [105]	56	13
2	Grattan [117]	114	12
2	Lin *et al.* [106]	29	12
2	Li *et al.* [99]	88	12
2	Lonstein and De Vries [108]	64	11

5.1.3. Cluster #1: “Medial Preoptic Area Interaction"

In Table 6, the most active citing documents for cluster #1 are reported. As suggested by the name of the cluster, and anticipated by the previous one, the interest of researchers in those years was oriented towards expanding the focus of attention towards a circuit, and not only a single area, controlling parental behavior. For these reasons, researchers started to look at the interactions between the MPOA and other brain regions in order to better understand the regulation of parental behavior [118]. To do so, Numan *et al.* [32] hypothesized that the way in which the MPOA facilitates maternal behavior in rats involves circuits of inhibition [119]. In fact, the MPOA forms connections with the nucleus accumbens, which exerts inhibitory GABAergic control over the ventral pallidum, a central region involved in eliciting maternal responses in response to pup stimuli. For the authors, the MPOA facilitates maternal behavior by inhibiting the nucleus accumbens and, therefore, indirectly activating the ventral pallidum. In support of the role of the nucleus accumbens in maternal behavior, the study by Olazabal and Young [120] showed that oxytocin receptors in this brain region, whose expression increases in the MPOA and other areas after parturition [121–124], is related to the expression of spontaneous maternal behavior in prairie voles. In the same way, dopamine D1 receptors antagonists disrupt retrieval and licking of pups in rats when injected in the nucleus accumbens [44,125,126], and also in the MPOA [127]. The region of the nucleus accumbens critical for pup-retrieval behavior seems to be the shell [128], which seems to be involved in the consolidation of maternal memory [129,130]. Even with some subtle differences, dopamine receptor antagonists modify parental behavior even in prairie voles [131]. Dopamine in the nucleus accumbens was also linked to rats’ maternal behavior [132], specifically, pup licking/grooming [33]. Based on this evidence, some authors suggested that the neural system controlling maternal behavior in rats could overlap with the dopamine circuit of rewards in the brain [133–136]. The neural model designed to explain the mechanisms with which the MPOA controls maternal behavior included two paths of actions [35]. In the first one, the activated MPOA would inhibit a central aversion system responsible for defensive and avoiding behaviors towards pups. In the second, the MPOA would act by exciting the mesolimbic dopamine system in order to promote voluntary maternal responses [137–139]. Therefore, some references within the cluster were cited because they explored the properties of the dopamine mesolimbic circuit [140–146]. The neural model of maternal behavior was refined in the review written by Numan and Stolzenberg [31]. Here, the authors discussed the interaction between the dopamine system and the MPOA [147]. In particular, they reported findings suggesting that the MPOA activates the shell region of the nucleus accumbens through mesolimbic dopaminergic inputs in order to control aspects of maternal appetitive behavior [41]. To facilitate the effect of the MPOA on the nucleus accumbens, dopamine from the incerto-hypothalamic system interacts with steroid and peptide hormones to finally act on the

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MPOA [148,149]. For this reason, part of the references in the cluster were cited because they studied the effects of steroid or peptide hormones on parental behavior [113,117,150–157]. As a matter of fact, some of these molecules seem to be crucial for maternal aggression aimed at protecting offspring [158–163]. If dopamine levels in MPOA seems to increase during lactation [164], the neural origin of such molecular inputs was debated. For instance, Miller and Lonstein [165] did not find a significant number of dopaminergic cells arriving at the MPOA from the zona incerta of the brain, but found them in other brain regions, such as the ventrocaudal posterior hypothalamus, the medial supramammillary nucleus and part of the ventral tegmental area. In fact, the causal role of the ventral tegmental area, a crucial area in the mesolimbic circuit whose activity is regulated by GABAergic and glutamatergic connections from the bed nucleus of the stria terminalis [166–168], in maternal behavior is documented by Numan *et al.* [169]. In this regard, a temporary inactivation of the ventral tegmental area in postpartum female rats interferes with the preference for pup-paired context in a conditioned place preference paradigm and reduced pup licking and pup retrieval behaviors [170]. In the same way, the inhibition of the medial prefrontal cortex negatively affected the pup retrieval behavior in maternal rats [171]. The motivational perspective on the female's response to her offspring started to grow following the trend of research in the 2010s. It became clear, in that period, that immediately after parturition, several brain structures (including the MPOA) contribute towards inducing a pup-specific bias to the motivational circuitry [16,39,172,173].

Table 6. Major 10 citing documents in cluster #1 identified using the DCA.

Cluster	Citing Document	GCS	Coverage
1	Gammie [118]	69	25
1	Curtis *et al.* [174]	57	19
1	Numan [35]	159	17
1	Numan and Stolzenberg [31]	224	17
1	Numan *et al.* [126]	119	15
1	Numan and Woodside [172]	89	15
1	Pereira and Morrell [39]	84	14
1	Perrin *et al.* [175]	37	14
1	Numan *et al.* [32]	91	14
1	Olazabal and Young [120]	176	12

5.1.4. Cluster #0: "Parental Behavior"

In Table 7, the most active citing documents for cluster #0 are reported.
In particular, Rutherford *et al.* [176] followed the approach of research suggesting the involvement of the reward system on parental behavior [46,132,177,178]. By using a place preference method, Mattson and Morrell [179] found that the MPOA was the only area showing a larger activation when dams preferred pup-associated versus cocaine cues, a preference that has been replicated in the literature [180,181]. In this rewarding process, oxytocin is a molecule that, for its role in social cognition and social rewards [182], plays a role in the stimulation of dopamine in the mesolimbic system, making child stimuli more rewarding [38,183]. During 2010s, it became evident that maternal experience also has a role in regulating behaviors targeted at caring for offspring [184]. For instance, the dopaminergic response to pup-exposure in the shell of the nucleus accumbens depends on the female's experience with pups, with higher experience associated with higher levels of dopamine [185]. In fact, the mesolimbic pathways sustain the changes due to maternal experience, with both dopamine receptor subtypes in the nucleus accumbens allowing the consolidation of this experience-dependent memory [186]. Olazábal *et al.* [187], by proposing new models to explain maternal behavior in different species and contexts, highlighted the flexible role of the MPOA in such neural circuits, an area that seems to facilitate maternal behavior during the early postpartum period and inhibit it in the later

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postpartum [188]. This transient role within the motivational system that the MPOA plays in the regulation of parental behavior is also detected in the available literature on the topic [39]. A final aim of the work by Olazábal *et al.* [187] was to extend the knowledge obtained from other species to human mothering. This intent, as in other works in the literature [189], was pursued also by Lonstein *et al.* [190], who compared the evidence on the biopsychological influences that regulate maternal behaviors obtained from studies on animal models (mainly rats and sheep) to extend the understanding of human maternal behavior. The authors of this review reported many similarities and differences in factors influencing mothering among species. The differences would be linked to species-specific features, such as the role of hormones, of each sensory system, the flexibility in behavior, whether there is a language or not, and the role of cortical functions. These evidence led many researchers to explore the mechanisms underlying postpartum neuropsychiatric disorders, which are reported by many women. In particular, the review written by McHenry *et al.* [191] studied the changes in reproductive steroids in order to activate maternal behavior and their association with postpartum neuropsychiatric disorders in many women, especially affective disorders [192,193]. The authors suggest that many brain regions, including the MPOA and the ventral bed nucleus of the stria terminalis, could mediate these effects for their influences on motivation and anxiety during the postpartum period [191,194]. This influence of the MPOA and the bed nucleus of the stria terminalis appears to depend on maternal experience [175]. In fact, maternal memory, which in part depends on amygdaloid V1a receptors [195] and the nucleus accumbens shell [196], is known for influencing the female's behaviors towards pups in rats [197]. This is not surprising, for the hippocampus is a plastic brain structure whose attributes vary with pregnancy or mothering [198,199]. For this interest, studies investigating the properties of plasticity within the hippocampus and other brain regions, such as the MPOA, were included in the cluster [200–204]. An insight on postpartum mood disorders following alterations of the maternal neural systems was also given by other references in the cluster [40,205,206].

Another trend of research within the cluster looked at the fact that lactating dams are less fearful than non-maternal animals and they exhibit lower hypothalamic–pituitary–adrenal (HPA) activation in response to potential environmental threats [207]. The diminished responsiveness of the HPA axis, which leads to a general sense of calmness in mothers, are due to the modified activity within two systems: a circuit that inhibits the HPA axis (e.g., oxytocin and prolactin systems) and another one with excitatory effects on the HPA axis. The first one would see an increased activation during lactation, whereas the second one would see a reduction in its activity [208]. The review by Bosch [209] was focused on the role that the reduction of anxiety in lactation plays in maternal behavior. In fact, high innate anxiety in dams tends to lead to intense and protective maternal behavior alongside an increased aggression towards a virgin intruder. Such behavior is considered functional to protect the pup against infanticide. Oxytocin and vasopressin are involved in this process reported in the review [42,210–212]. As a matter of fact, the release of these molecules in areas such as the hypothalamus and the limbic system contributes to the regulation of maternal behavior, including maternal anxiety and aggression [148,163,213–224]. For this interest, some references within the cluster were cited because they studied the mechanisms of action of those molecules [47,225–230]. Specifically, the mother's brain sees an increased release of oxytocin during breastfeeding. When functional magnetic resonance imaging is used on dams, the brain's pattern of activation following administration of oxytocin overlaps with the pattern of activation during pup suckling. This pattern included brain regions known for their role in regulating olfactory discrimination, emotions and reward [231]. Moreover, pup suckling activates multisensory processes in the brain of lactating dams [232,233]. In the review by Dobolyi *et al.* [234], authors focused on the role of the input from pups that activate the MPOA and, therefore, maternal behavior. The authors discussed that, in rodents, neurons containing the tuberoinfundibular peptide of 39 residues in the posterior thalamus appear to be good candidates to convey the suckling

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information to the MPOA, supporting maternal responsiveness. The way in which these inputs influence the neurons in the MPOA seems to depend on modifications of the gene expression, which seem to support maternal behavior [235–237]. In particular, chromatin remodelling mediates these alterations in the long-term [238,239].

Within this cluster, Tsuneoka *et al.* [34] studied the subregions in the MPOA that are necessary for maternal behavior in mice. Their results showed that the central part of the MPOA is crucial for maternal behavior, for its lesions lead to infanticide. Moreover, this subregion of the MPOA shows a c-fos activation during maternal behavior mostly in regards to GABAergic and peptidergic (galanin, neurotensin, and/or tachykinin2 mRNAs) neurons, as in other studies [8]. Alongside this interest on deepening the understanding of the role of the MPOA in female parental behaviors, some authors within the cluster tried to examine whether such knowledge could be applied to males' parental behavior [240,241]. As a matter of fact, males do not meet the hormonal cascade at a female's parturition, postpartum ovulation and lactation. Nevertheless, in new fathers, the MPOA, the bed nucleus of the stria terminalis and the caudal dorsal raphe nucleus are activated in response to pups [242,243]. As in females, paternal experience in rodents is associated with a diminished activation in fear/anxiety brain regions and an increased activity in the network responsible for affiliative responses, which included the MPOA [244]. Upon becoming parents, male rodents have to inhibit the mechanisms responsible for infanticide and activate direct parental behavior towards the offspring. Evidence showed that the downregulation of the activity of neurons along the vomeronasal system, mainly sensitive to olfactory stimulus, is responsible for the shift from aggression towards pups in sexually naive male mice to the display of paternal behavior in fathers [245]. Nevertheless, virgin males' aggressive behavior guided by the activity of the vomeronasal system seems to rely on the morphological features of the pup and salivary chemosignals [246]. Similar to female rodents, the central part of the MPOA plays a crucial role in parental behavior in male rodents, alongside the bed nucleus of stria terminalis. In fact, Tsuneoka *et al.* [48] showed that the activity in these two brain regions was able to detect paternal and infanticidal motivation with high accuracy (95%). Furthermore, lesions of the central MPOA induced infanticide, whereas lesions of the rhomboid nucleus of the bed nucleus of stria terminalis showed the opposite pattern, inhibiting infanticidal behaviors in virgin males. Moreover, the expression of androgen receptor and estrogen receptor (ER) α and their interaction with testosterone is fundamental for males' sexual, aggressive and parental behaviors. This expression depends on the neuronal subtypes and the subregions examined in the MPOA [247].

Table 7. Major 10 citing documents in cluster #0 identified using the DCA.

Cluster	Citing Document	GCS	Coverage
0	Lonstein *et al.* [190]	62	31
0	Numan and Young [248]	131	23
0	McHenry *et al.* [191]	20	20
0	Olazábal *et al.* [187]	55	18
0	Dobolyi *et al.* [234]	40	18
0	Yoshihara *et al.* [224]	15	18
0	Rutherford *et al.* [176]	81	17
0	Bosch [209]	100	16
0	Bridges [40]	146	16
0	Numan [249]	0	16

5.2. Keywords Analysis

The analysis of the keywords with a citation burst supports the trends of research that emerged from the analysis of publications composing the network's clusters. In particular, besides the keywords indicating the brain region of interest for the specific studies (*central nervous system*, *hypothalamus*, *medial preoptic area*, *preoptic area* and *brain*), the other indexing

 doi:10.20944/preprints202102.0612.v1

terms mostly referred to the methodology used to investigate the relationship between the MPOA and parenting. As observed from the results, the vast majority of studies in the field was conducted on rats using methods to analyze protein expression within the brain. Also, as emerged from the discussion on clusters, most of the studies focused on the period of time around pregnancy (pre- and postpartum). Furthermore, although the majority of the studies exploring the role of the MPOA in parenting were conducted on females, research interest has recently involved males and paternal behavior as well.

6. Conclusion

In this paper, we used a scientometric analysis to identify research trends in past publications investigating the association between the MPOA and parental behaviour. We found four major clusters that characterised significant time periods in this dynamic area of research in order of chronology: “C-Fos Expression", “Lactating Rat", “Medial Preoptic Area Interaction" and “Parental Behavior". Initial research interest focused on examining an established physiological response in the brain associated with the maternal response (first cluster) and then, mainly by the study of lactating rats (second cluster), new models to explain maternal behavior were conceptualised. Subsequently, equipped with insight gathered from these new models, researchers turned their focus towards investigating brain circuitry beyond just the MPOA in controlling parental behaviour (third cluster). Finally, the most recent predominance in research looks at disentangling the many aspects of parental behaviour, including paternal behavior and infanticide (fourth cluster). The keyword analysis also identified terms, especially those associated with brain regions and methodology, that extend beyond the clusters, revealing possible foundations for subsequent research contributing to this line of work.

This study has some limitations which we outline here. Firstly, The publication sampling method employed specifies a constraint of identified keywords to be present in the titles, which, though it has the obvious advantage of streamlining the selection process, excludes relevant publications which may not have been captured [250]. Consequently, underlying themes in the research not reflected in the publication titles, abstract or keywords may have been overlooked. Next, only a few keywords were used to extract source articles from a single database, Scopus. Extensions of this work may consider using alternative keywords and including other databases (e.g. Web of Science) to determine whether the pattern of results hold. This specific scientometric approach may also be unable to fully encapsulate the extent of the trends in this research, particularly in view of unpublished works [251].

Another limitation of the scientometric approach is that it strongly relies on citations among documents. This method gives insight into the trends of research, but it does not capture the specific nature of the relations among co-cited papers. Analysing citations among documents leads to a bias towards past publications. In fact, documents published in the past tend to have higher number of citations as compared to more recent ones. This difference in the number of citations between past and recent publications would not reflect a difference in importance and scientific impact, but a difference in the “years of life" of a publication. A final and more technical limitation is that the references within the file downloaded from Scopus were not always consistent in the way they are cited by other publications. Sometimes this leads CiteSpace to consider two formats of citation of the same reference as two different publications. For this reason, some documents appear more than once within a cluster or even within the network.

The role the MPOA plays in parental behaviour continues to be a dynamic area of research. Historically, there has been a large focus on parental behaviour in mothers, particularly in the pregnancy or lactating stages of motherhood, for the role of the hormones associated with those phases. As seen in the fourth cluster, there is a growing trend in research investigating infanticide and paternal behaviour. Future work may build on this relatively recent development and use the findings in this paper as a guide in the literature exploring the role of the MPOA on parental behaviour. This line of research in

 doi:10.20944/preprints202102.0612.v1

paternal behaviour could lead to the elucidation of the underlying basis of sex differences in nurturing behaviors among parents, particularly sexual dimorphisms in the brain. Nonetheless, continual work in examining the neural correlates of maternal behaviour has relevant practical implications in understanding the driving factors predisposing many women to experience neuropsychiatric conditions in the postpartum period, namely depression [252].

Author Contributions: Conceptualization, G.E. and A.C.; methodology, A.C.; formal analysis, A.C.; investigation, A.C.; data curation, A.C.; writing—original draft preparation, A.C., J.P.M.B. and M.J.Y.N.; writing—review and editing, A.C., J.P.M.B., M.J.Y.N. and G.E.; visualization, A.C.; supervision, G.E.; funding acquisition, G.E. All authors have read and agreed to the published version of the manuscript.

Funding: This research was supported by grants from the NAP SUG to GE (M4081597, 2015-2021).

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

The following abbreviations are used in this manuscript:

DCA	Document co-citation analysis
Fos-ir	Fos-immunoreactive
Fos-lir	Fos-like immunoreactivity
HPA	hypothalamic–pituitary–adrenal
MPOA	Medial preoptic area

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 doi:10.20944/preprints202102.0612.v1

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