MASTER ESSAY

The influence of social housing on behaviour and brain plasticity in rodents

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The influence of social housing on behaviour and brain plasticity in rodents.

Foreword

This essay was commissioned by the master Biomedical Sciences of the RUG. Because of the interest in Behavioural Neurosciences, there is chosen for a Neurobiological subject. Subject of social housing and changes in behaviour and brain plasticity in specific was chosen because of a recent article published on ScienceDaily by the University of California – San Diego. On March 5th 2021 they published, "*how does your brain process emotions? Answer could help address loneliness epidemic"*. Currently, we live in a pandemic where people are socially isolated. Better understanding of the effects of social isolation or enrichment on the brain and its function in animal models could help in addressing the loneliness in people caused by the pandemic.

Abstract

Social isolation, loneliness and their effects on health and the brain are more applicable than ever because of the global pandemic caused by COVID-19. Billions of people are quarantined in their own homes as different governments have announced a lockdown causing many people to be socially isolated. Social isolation in rodent models can have negative effects on both the brain and rodent behaviour. Examples of changes in the brain are alterations in the hippocampal CA1 region and the glutamate-GABA cycle. Changes in behaviour may cause an increase in the risk on diseases such as Schizophrenia, depression/anxiety disorders, seizures and epilepsy. On the contrary, environmental enrichment can have positive effects on behaviour, hippocampal CA1 neurons and the glutamate-GABA cycle by counteracting for the damage done by social isolation. Environmental enrichment could also help in the treatment or possibly prevention of autism spectrum disorders, Alzheimer's disease and seizures. This indicates the importance of social/environmental enrichment and the risks that can be induced by the social isolation during this time of the COVID-19 pandemic.

In this thesis

Introduction

Social isolation, loneliness, and the effects on health and the brain are more applicable than ever because of the global pandemic caused by COVID-19. Billions of people are quarantined in their own homes, not only when they are infected with the virus but also to prevent further distribution. Different governments have also announced a lockdown, setting different rules which causes many socially isolated people (D. Banerjee, 2020).

Social isolation is a recognized risk factor in health, morbidity, and mortality for a long time. Positive social stimuli, such as friends and family, encourage the development of great health behaviours. Where negative stimuli encourage the development of bad health behaviours such as smoking or excessive eating. The brain is a key organ here, and not only responds to these stimuli but also categorizes, abstracts, interprets and evaluates all these stimuli. Loneliness is a factor that could increases attention to negative social stimuli and have negative impact on health (J. T. Cacioppo, 2015). Research of the university of California – San Diego substantiates the idea that loneliness can increase the attention for negative stimuli. *G. Grennan, et al* have found that lonelier (scored by the UCLA-3 Loneliness Scale) individuals were more sensible to negative stimuli, such as angry faces, than wiser (scored by the SD-wise scale) individuals. Where wiser individuals were more sensible to positive stimuli, such as happy faces, than lonelier people. They state that these findings could be relevant in mental and physical health because it gives an insight how lonelier (or wiser) individuals process information (ScienceDaily, 2021) (G. Grennan, 2021).

The effects of such social isolation on the brain can be studied in two ways, using human or animal studies. The advantage of animal studies over human studies is the ability to manipulate the social isolation and the environmental factors (J. T. Cacioppo, 2015). The goal of this essay would be to use animal study-based literature to answer the question: **What effect do social isolation and environmental enrichment have on behaviour and brain plasticity?** This will be done by discussing three sub-topics that relate to social isolation, behaviour and brain plasticity. The first subject will be the behavioural changes seen in rodent models of social isolation and environmental enrichment. The second one will be the effect of (non)social housing on the hippocampal CA1, region and the last one would be the effect of (non)social housing on the glutamate - Gamma-Amino Butyric Acid (GABA) cycle/genes.

Environmental enrichment and behavioural health of rodents

Environmental enrichment is a manipulated type of environment used for the wellness of animal models. Enrichment means adding physical and/or social elements that stimulate non-aversive behaviour (J. E. Sparlinga, 2020). This will protect against the development of behaviour associated with mental illness (S. Baldini, 2013), promotes healthy physiological responses (A. L Smith, 2005), and could be neuroprotective (A. C. Kentner, 2019). Studies show that rodents exposed to environmental enrichments and socially isolated rodents show a difference in their behaviour. These differences are seen in anxiety-like behaviour, depressive-like behaviour, maternal caregiving behaviour and maternal anxiety (J. E. Sparlinga, 2020). Environmental enrichment can include a higher number of animals per cage or even a mirror to simulate social interaction. Social interaction often has positive effects on exploration an anxiety of rodents. Greater performance of enriched animals in cognitive and behavioural test is toughed to be related to changes in the structure and functioning of the brain (P. Sampedro-Piquero A. B., 2017). Environmental enrichment increases the volume of the hippocampus (M. C. Diamond, 1976) among other structures. Not only brain structures are altered but also the neurogenesis resulting in an increase of neurons in the hippocampus (E. Castilla-

Ortega, 2010). Examples of these changes in the structure of the hippocampus and the neurogenesis are discussed later.

Mice can best be kept in a social housing however individual housing can be necessary, like after surgery for example. When comparing both in behavioural investigations *Jirkhof and colleges* found slight tendencies towards better wellbeing in social housing and no adverse effects such as aggression in mice. However, in the context of reducing surgical stress or improving postsurgical recovery, they were not able to significantly show that social housing is superior to individual housing (P. Jirkof, 2012). *Van Loo* however did show the importance of social interaction for mice. In his research social housing has a positive effect on post-operative recovery. So social housing indeed could be of great importance for the animals bit as said this is not always possible. An alternative for social housing would be "living apart together" (LAT) housing, where mice were separated by a grid. LAT housing is an improvement on individual housing and comes closer to the environment of social housing but it showed not to be necessarily better than individual housing (P. L. P. Van Loo, 2007). Indicating the importance and irreplaceability of social housing and interaction.

Early life environmental enrichment

Environmental enrichment can be induced at different timepoints in life. Starting in early life, research has shown behavioural differences between social and individual housing. *I. Branchi and colleges* for example found difference in behaviour between standard nesting (SN) and communal nesting (CN) mice. In communal nesting the maternal care-giving behaviour is divided between multiple mothers instead of one. When pups are raised in the CN environment it enhances their social interaction and shapes the social competencies (I. Branchi, 2006). Similar research on pups raised in SN vs CN shows that the environmental enrichments or experiences in early life interact with gender in forming the adult behaviour. This interaction with gender is seen in female mice which show a higher vulnerability for depressive-like behaviour, also in relationship with early life experiences. SN female mice are for example more vulnerable for the development of depressive-like behaviour than SN male mice. However, CN female mice do have a lower vulnerability for developing depressive like behaviour in comparison with the SN female mice (I. D'Andrea, 2010). More recent research has shown the importance of social enrichment for the development of social skills. *M. Toyoshima and colleges* compared the effect of social enrichment on both social and non-social memory tasks with the use of the Different Object Task (DOT) and a multiple social discrimination test (MSDT). The tests show that social enriched housed mice were the only group exploring new conspecifics and where able to memorize the five conspecifics of the sample phase. The socially isolated and standard housed where not able to identify the new conspecifics. Indicating that social enrichment enhances the social memory span. In the DOT performance was not different between the social enriched, socially isolated and standard housed rodents. So, they concluded that social enrichments of rats can enhance the social memory span, but not the object memory span (M. Toyoshima, 2018). Overall, the conclusion is that early life environmental enrichment such as social interaction is important in the development of social skills and in the prevention of diseases such as depression.

Maternal environmental enrichment

Environmental enrichments are not only of influence in early life but also during pregnancy and parturition. Pregnancy can be seen as an enrichment itself and during pregnancy there is a positive relationship between neuroendocrine changes and the development of motherhood behaviours (J. Kohl, 2018). Environmental enrichment before and during pregnancy can have multiple effects. Female, future mothers, exposed to environmental

enrichment show improvement in spatial learning tasks. Even though, effects on anxiety like behaviour are not always found (A. R. Zuena, 2016) some research did show reduced anxious behaviour in their animals (P. Sampedro-Piquero, 2014). Also changes in maternal behaviour are seen, where mothers spend less time nursing for example (P. Sampedro-Piquero, 2014). But not only mothers' profit from the "enrichments" provided by pregnancy. The rodent mother-pup relationship is important for both of their health (J. E. Sparlinga, 2020). In the offspring of environmental enriched mothers an increase of social play behaviour is seen, mainly in males. Female offspring did not show an increase in social play behaviour however they did show improvement in spatial learning. Anxiety like behaviour is not only altered in the mothers but male offspring also show a decrease in anxiety like behaviour. The only thing that was altered in both gender offspring was the motility in behavioural tests. This research indicates that importance of maternal environmental enrichment however it also shows a possible gender related difference in the influence on offspring (P. Sampedro-Piquero, 2014). So, pregnancy and the environmental enrichment coming with it is both important for mothers as well as for their pups.

Hippocampal CA1 and the influence of environmental enrichment

Environmental enrichment is not only of influence on behavioural health but also on the development and functioning of the brain. Enrichment has shown to be beneficial to the nervous system in a variety of species (Abraham M. J., 2012). One of the brain regions effected by environmental enrichment is the CA1 region, one of the hippocampus's main output structures (K. Nakazawa, 2004). The CA1 region has an information processing role, as it could be important in determining whether an object is contextual or novel. The CA1 region also could play a role in the consolidation and retrieval of recent contextual memory rather than in the initial processing (S. Daumas, 2005). The neurogenesis and plasticity of adult hippocampus regions are dependent on two different factors. One being genetic which will not be discussed at this point, the other one being environmental factors (L. Lu, 2003). In the section below, we will discuss the effects of social isolation and enrichment on the CA1 region of the hippocampus. These effects could be divided into different subcategories: synaptic transmission, Synaptic plasticity and physiology of the hippocampus (Abraham S. M., 2018).

Synaptic transmission

In the CA1 region synaptic transmissions take place in the Schaffer collateral pathway. Schaffer collateral evoked responses from area CA1 can be recorded using stainless steel wire recording and stimulating electrodes that are implanted. In cases of environmental enrichments for 2 or 3 times a week, different research has shown to have either no change or a slight decrease in transmission of the synapse (Abraham S. M., 2018). However, there is some research showing otherwise. *G. I. Irvine and colleges* found that with high stimulus intensity environmental enrichment can refine the Schaffer collateral synaptic transmission by making it more receptive during periods of high synchronous afferent activity (G. I. Irvine, 2005). Despite the contradicting results research does show that the Schaffer synaptic pathway could be altered by environmental enrichment.

Synaptic plasticity

L. Lu and colleges used a water maze task for spatial learning and electrophysiological research using different electrodes to determine the hippocampal Long-Term Potentiation (LTP), a model for synaptic plasticity, to analyse the influence of early life isolation on neurogenesis and neuroplasticity of the hippocampus. When looking at the hippocampal CA1 region the results show that isolation rearing reduces LTP but that this effect can be reversed by group rearing (L. Lu,

2003). The effects of environmental enrichment are, even though expected, not always found. *M. J Eckert* and colleges did not find differences in LTP measures in the CA1 region for example. But they were still able to make a similar conclusion concerning the plasticity of the CA1 region being influenced by short term environmental enrichment. They found alterations in plasticity of the CA1 region in the parameters long-term depression (LTD) and the amount of depotentiation in stratum oriens (M. J. Eckert, 2010). LTD and LTP, both factors of great interest, can be influenced by enrichment in multiple ways. The plasticity processes may be improved, resulting in more LTP/LTD being induced or lasting longer. Synaptic strengthening induced by environmental enrichment can result in the occlusion of future LTP. But lastly, as mentioned earlier it also could be that environmental does not have an effect on LTP/LTD (Abraham S. M., 2018). So, there could be concluded that it is not clear if environmental enrichment has an influence on LTP/LTD and therefor synaptic plasticity.

Physiology of the hippocampus

The hippocampus of environmental enriched rats uses sparser neural representation for encoding a novel environment. This makes a network able to store more data and discriminate patterns easier, which could explain the cognitive benefits of social enrichment (M. J. Eckert, 2010). The remodelling of neurons (in female rats) during adolescence differs between dendritic arbor and spines of pyramidal cells in the dorsal hippocampus, and those in the ventral hippocampus CA1 region. Main differences are dendritic complexity and dendritic spine density. Dendritic complexity in the dorsal hippocampus decreases during development where it increases in the ventral hippocampus. Dendritic spines mature, but do not change in density in the dorsal hippocampus during adolescence. In the ventral hippocampus the density does change by increases and show also more mature spines during adolescence. Data of *Chen and colleges* shows that when rats are pair housed the dendritic branching of dorsal hippocampus is increased and that of neurons in de the ventral hippocampus decreases. This shows how neuronal development in the CA1 region can be altered during adolescence by environmental changes, isolation in specific (Y. Chen, 2018). These alterations can be imaged and reviewed with the use of Cresyl-violet staining on the hippocampal tissue. When looking at the volume of the hippocampus and its specific regions such as CA1 but also CA3 differences between social isolated and non-isolated animals are seen. Only the volume of the CA1 region reduces in volume when female degus are isolated (I. Pereda-Pérez, 2013).

Social housing and the glutamate GABA cycle

Since there are synaptic changes seen in the CA1 hippocampal region in social isolation and environmental enrichment the next step would be to look an essential pathway of synapses. Part of this essential pathways are essential amino acids (AA) glutamate and GABA, which function as excitatory and inhibitory neurotransmitters. Both neurotransmitters are of great importance in the formation and processing of memory. Which makes research on their function on learning and memory of great interest (S. Tabassum, 2017).

The glutamate and GABA neurons are essential for interaction between a glutamatergic neuron and an astrocyte and the interaction between an astrocyte and the GABAergic neuron. For the brain metabolism a compartmentation theory was developed. In this theory there are multiple pools of metabolites in neurons and astrocytes. The reason for these different pools is the observation of different basic metabolites in both neurons and astrocytes. In figure 1 the interaction between different compartments, being a glutamatergic neuron, an astrocyte and

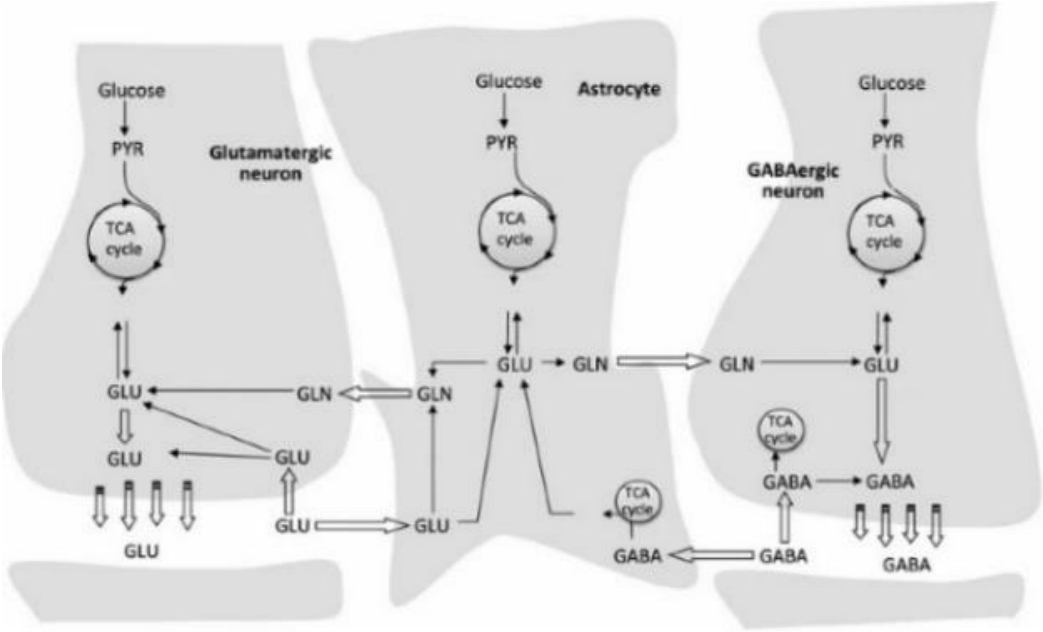

Figure 1: Schematic representation of the glutamate-GABA cycle used in interaction between glutamatergic neurons, GABAergic neurons and astrocytes. GLN glutamine, GLU glutamate, PYR pyruvate carboxylase, TCA tricarboxylic acid. Figure based on: (A. B. Walls, 2015)

the GABAergic neuron is shown. First you have glutamate, a neurotransmitter that is formed out of glucose converted to Pyruvate carboxylase (PC) to glutamate via the tricarboxylic acid (TCA) cycle. Glutamate travels from the presynaptic glutamatergic neuron towards the postsynaptic membrane to interact with receptors to be transported into the astrocytes. The loss of glutamate in neurons can be refilled by the transformation of glutamate into glutamine (GLN). This glutamine can be transported from astrocytes towards neurons where it can be converted back to glutamate and again function as a neurotransmitter. In this way a homeostasis of the glutamate neurotransmitter in both glutamatergic and GABAergic neurons is established. In the GABAergic neuron's glutamate is formed in the same way as in the glutamatergic neuron, via glucose to pyruvate carboxylase to glutamate in the TCA cycle. In the GABAergic neuron glutamate is not used as the eventual neurotransmitter, but is transformed to the neurotransmitter GABA. GABA in the extra synaptic space is either transported back into presynaptic neurons or for a smaller part to astrocytes (A. B. Walls, 2015).

The Glutamate part of the glutamate-GABA cycle

Glutamate, or rather its metabotropic receptor (mGlu), is of great importance in the early mentioned altered plasticity of synapses. The plasticity in the hippocampus is essential for the formation of memory (T. Takeuchi, 2014). As mentioned earlier the hippocampal LTP is a factor influenced by environmental enrichment and is also associated with memory (H. Hagena, 2011). The importance of mGlu5 in synaptic plasticity and memory sparked an interest because of the possibility of its influence in the improvement of LTP. Research shows that mGlu5 indeed is of importance in LTP of young mice. In fact, early and late phases of LTP require mGlu5. In older rats the mGLU5 is however not crucially required for LTP. So, it was found that the enhancement of LTP caused by environmental enrichment requires the presence and activation of mGlu5 (A. Buschler, 2017). Those glutamatergic receptors are of great importance in memory and the positive effects of environmental enrichment is

substantiated by research in cognitive impaired mice. Glutamatergic systems are inhibited when the hippocampus is injured. After injury cognitive functioning recovery is promoted by environmental enrichment trough upregulation of glutamatergic genes (Y. Wang, 2020). In post weaning socially isolated male rats the expression of a big part of the glutamatergic receptor genes is 1.5-fold increased in the CA1 and CA3 hippocampal cells (H. Iwata, 2016).

Knowing that glutamate receptors and related genes are influenced by environmental enrichment and social isolation the next question is; what happens to the neurotransmitter glutamate itself. Environmental enrichment seems to change levels of neurotransmitters (D. S. Alwis, 2014). Research on glutamate in environmental enriched and isolated environment is quite indecisive. *G. Segovia and colleges* found that the basal and stimulated levels of the neurotransmitter glutamate were increased in social housed older rats (G. Segovia A. G.-v., 2006). Where *E. J. Conners and colleges* found that the basal hippocampal glutamate shows no difference in pre- and post-weaning environmental enriched or communal nested rats (E. J. Conners, 2015). Concluding it is clear that social isolation and environmental enrichment are of influence on glutamate, it's receptor and it's encoding genes however it is not clear what the exact effect would be as literature is quite contradictive.

The GABA part of the glutamate-GABA cycle

The activity and expression of GABA receptors in the rat's hippocampus are selectively modulated by physiological and pharmacologically mediated variations in brain concentrations of neuroactive steroids, such as those that occur throughout pregnancy and pseudopregnancy. Similar results are seen when looking at long-term isolated rats. *M. Serra and colleges* found that the social isolation changed the emotional behaviour, induces decreases in neuroactive steroids of both brain and plasma origin, and induces a decrease in brain $GABA_a$ receptor functioning (M. Serra, 2000). The reduction in GABAergic functioning seen in social isolated animals could be caused by the greater activity of GABA Transporter Type 1 (GAT-1). Even though GABAergic neurons seem to hypofunction an upregulation of the GABA receptor expression is seen, possible as a compensatory mechanism for the decrease in GABAergic neurotransmission (A. J. Hickey, 2012). However other research shows a decrease of $GABA_A$ receptor unit gene expression in the CA1 and CA3 region of the hippocampus. Together with the increase of glutamatergic gene expression this shows that the hippocampal region of socially isolated rats is in a more excitable state than that of group housed rats (H. Iwata, 2016). When comparing the changes of neurotransmitters such as GABA in young and older rodents' contradictory results are found in research. *G, Segovia and colleges* found that levels of not only glutamate but also that of GABA where higher in the hippocampus of socially housed older rats (G. Segovia A. G.-v., 2006). This indicates a possible way of compensating for the deterioration in the hippocampus. Normally higher concentrations in GABA are seen in younger rats, the reason it is also found in older rats could be caused by changes in the astrocyte network (A. Del Arco, 2003). An increase in the activity and/or number of astrocytes is a very common phenomenon seen in aging (G. Segovia A. P., 2001). That the higher GABA levels are normally seen in younger rodents is substantiated in research from *A. Mora-Callegos and colleges.* They found the highest levels of GABA in environmental enriched young rats, compared with the same age standard condition rats and both conditions in older rats (A. Mora-Gallegos, 2015). Again, possible effects of environmental enrichment on the GABA pathway are seen, however literature is contradictive on what the exact effects would be.

The effects of alterations in the glutamate-GABA cycle on learning and memory

The plasticity of hippocampal synapses and the glutamate-GABA cycle are of great importance in learning and memory as mentioned before. So, the alterations in the glutamate-GABA cycle caused by either social isolation or environmental enrichment could be also be of influence on learning and behaviour. When glutamate and GABA are orally supplemented, they alter the levels of glutamate and GABA are altered in the rat hippocampus. With the aid of behavioural tests (Novel object recognition test, Morris water maze, Passive avoidance test) the cognitive functioning of rat was addressed. Results show that mainly glutamate supplementation improved the memory performance (S. Tabassum, 2017).

If there is an influence on glutamate levels in isolated or enriched individual is not quite clear. However, when a decrease of glutamate is seen in socially isolated rats this is associated with oxidative stress in the hippocampus. This oxidative stress is in its turn associated with impaired spatial working memory (Y. Shao, 2015). When glutamatergic signalling in the hippocampus is reduced, this does not mean that glutamatergic signalling is reduced in the whole brain. Social isolation for example seems to potentiate glutamatergic signalling in the olfactory bulb. The increase and decrease of glutamatergic signalling in different brain areas causes an unbalance, which is associated with impairment of social memory persistence (A. F. Almeida-Santos, 2019). Because of the importance of mGlu5 in synaptic plasticity and memory it would be expected that when expression is decreased, different cognitive aspects would be affected. In fact, mGLu5 is of essence in spatial learning, contextual fear conditioning, inhibitory avoidance, etc. In mGlu5 receptor knockout models contextual fear conditioning and spatial water maze tasks are impaired (A. Simonyi, 2010). It is even the case that environmental enrichment improves the learning and memory of rats via an essential signalling pathway using mGlu5 (R. Hullinger, 2015).

Whether GABA receptors are increased or decreased is not quite clear, however it is the case that when $GABA_b$ receptors are blocked it improves learning and memory. An antagonist of the GABA receptor was able to cause the retrieval of memory in mice, shown in different behavioural test (A. Almasi, 2018). This would mean that when GABA receptors are activated memory will be impaired. When using a GABA antagonist to activate the GABA receptors it prevents memory impairment (D. L. Krebs-Kraft, 2007). However, it is not clear what the influence of environmental enrichment or social isolation would be.

Discussion

The goal of this essay was to answer the question: **What effect do social isolation and environmental enrichment have on behaviour and brain plasticity? I** wanted to use rodent studies to see what the effects of social isolation and the benefits of environmental enrichment are. To do so, literature research on the effects of both aspects on behaviour, the hippocampal CA1 region and the GABA-glutamate cycle literature was done and is discussed in this essay. The influence of environmental enrichment is not only found in healthy rodents. An increase in the synaptic density as result of environmental enrichment has been reported in both healthy rodents (M. J. Eckert W. C., 2012), but also in different models for disease such as Alzheimer's pathology (K. E. Stuart, 2016). Here I will discuss the findings and its possible applications in disease treatment or prevention.

The first aspect coming forward is the effect of environmental enrichment on rodent's behavioural health. Both maternal and early life enrichment seem to be positively affected rodent behaviour later in life. Here will be discussed how environmental enrichment can also be beneficial in disease and disorders. In autism mouse models environmental

enrichment is used as a possible treatment. In autism spectrum rodent models phenotypes with anxiety-like behaviour, social deficits and cognitive impairment are seen. When these mice models are treated with environmental enrichment in early life, they show improvement in these cognitive impairments (H. Yamaguchi, 2017). There are not only genetic rodent models of autism but it can also be induced later on with for example valproic acid (VPA). VPA rats can be used as to analyse etiological, anatomical, and behavioural data in a model of autism. Comparing this model in standard condition with the same model in environmental enrichment shows that the environmental enriched VPA rat have higher sensibility to pain and lower sensibility to nonpainful stimuli. Among others, they also show increased number of social behaviour, lower repetitive/stereotypic autism-like behaviour, decreased anxiety and enhanced exploratory behaviour. This all makes environmental enrichment a possible tool in the treatment of autism spectrum disorders (T. Schneider, 2006). However more recent research does note, that even though environmental enrichment could be a good tool in autism treatment this not mean it will be a “one-size fits all” kind of treatment. In their autistic mice model environmental enrichment did not alter the repetitive behaviours and anxiety like behaviour was even increased (S. W. Hulburt, 2018). So even though social or environmental enrichment is of a positive influence on behaviour in both healthy as mentally disabled individuals it will not be applicable on every individual or every kind of behavioural disease.

Another thing that became clear was that the hippocampal CA1 region is both altered in social isolation and environmental enrichment. When the brain is damaged, for example in brain seizure, the structure and function of the hippocampus can be altered. It is shown that these damages can be restored or at least reduced by environmental enrichment. A mouse model showed reduced severity of seizure activity but also preserved LTP in the hippocampal CA1 region (E. Morelli, 2014). Similarly, results are seen in Alzheimer’s disease where despite the existence of accumulating Ab neuropathology, the CA1 region seems to maintain the potential for experience-dependent plasticity as a response to environmental enrichment (K. E. Stuart A. E.-M., 2016). Early-life enrichment may reduce the risk of cognitive deterioration and dementia in the future. However, it also seems to be the case that mid or later-life enrichment could promote synaptic and cognitive health. It even possibly could be that the capacity for synaptic connectivity promotion in ageing associated Alzheimer (K. E. Stuart A. E.-M., 2016). Showing that not only disease related behaviour, such as autistic behaviour, can be improved but also brain plasticity in both health and disease.

Lastly the importance of the glutamate-GABA interaction is discussed. It seems clear that social isolation and environmental enrichment are of influence. However, research differentiates in the results on levels of the neurotransmitters GABA and glutamate in both social isolation and environmental enrichment. These alterations in both neurotransmitters have influence on memory and learning either way, making it interesting to see what influence they could have in diseases encountering deficiencies in these factors. Huntington’s disease (HD) is a movement disorder which however does show memory and learning impairments. This impairments in a HD mouse model are partially caused by GABAergic inhibition. When this is restored memory deficits in HD are restored (Z. Dargaei, 2018). On the other hand, the opposite is seen in Alzheimer disease models. Astrocytes release an abnormal amount of GABA neurotransmitters, which alters the synaptic plasticity. When GABA production or release is blocked you see restoring of synaptic plasticity, memory and learning in mice (S. Jo, 2014).

Environmental enrichment can be beneficial and useful in the treatment of many diseases,

such as autism, Huntington's disease and Alzheimer's. The offset are the negative effects of social isolation which will be discussed next. Social isolation can cause a lot of stress in both humans and animals. This social isolation stress (SIS) is isolated with different modifications, as mentioned behavioural changes but also various diseases (F. Mumtaz, 2018). Early life SIS can induce the onset of emotional and affective disorders (N. R. Nugent, 2011). Later in life during adolescence the sensitivity to stress is at its peak which can possibly cause the development of neurobiological disorders such as schizophrenia (C. M. Hueston, 2017). In animal models exposed to SIS similar symptoms are seen as in humans with disorders as depression and schizophrenia (J. van Os, 2010). In fact, impaired sociability increases the vulnerability to social stress and alters a process called catecholaminergic intervention in brain areas, such as the hippocampal CA1, related to schizophrenia (S. Nullmeier, 2020). What became clear is that the social isolation can alter different behaviours, including anxiety and depressive like behaviours (J. L. Lukkes, 2009). In social isolated rodents' various symptoms associated with depressed patients are witnessed, indicating the risk of development of depression in social isolation (E. J. Nestler, 2010). Other conditions where SIS can be of influence are the risk for seizures (K. Matsumoto, 2007) and the severity of disease in epileptically patients (J. McCagh, 2009). Showing that social isolation is risk factor in the development of different diseases.

This essay indicates a small aspect of the influence of social isolation and environmental enrichment on behaviour and the brain. The hippocampus is not the only brain region altered by social isolation and deficits in other brain region can also have behavioural changes and disease as a result as can be seen in figure 2 (F. Mumtaz, 2018).

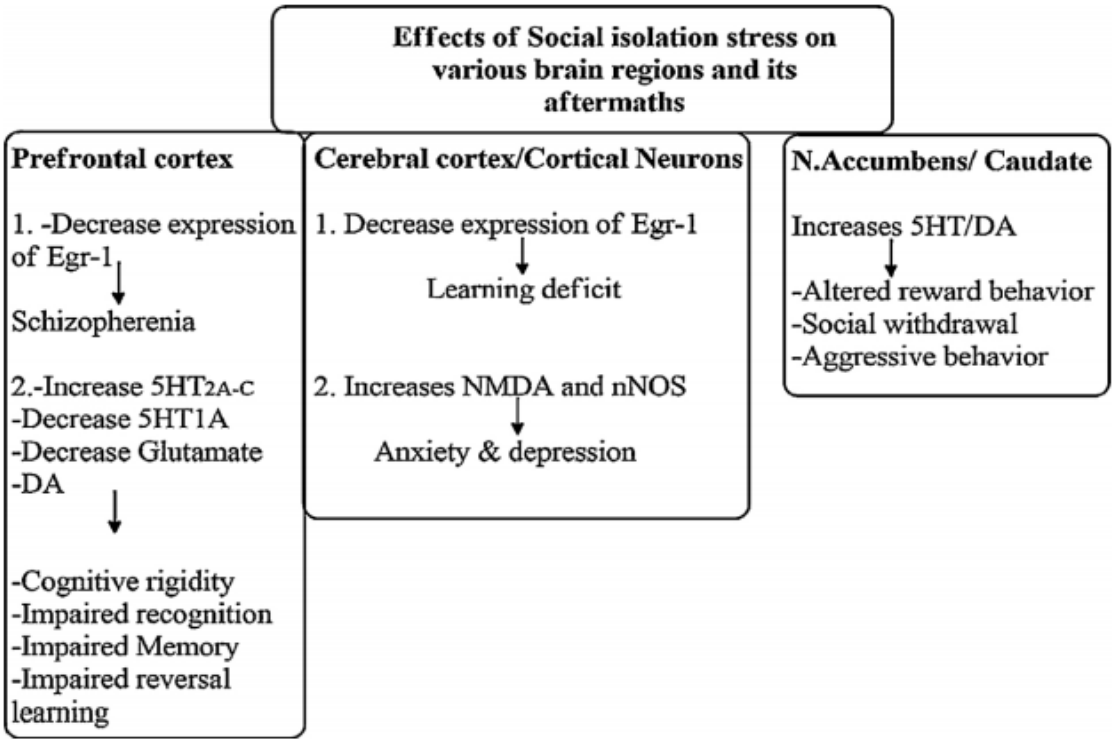

Figure 2: Multiple effects of Social Isolation stress and the various consequences.
Source: (F. Mumtaz, 2018)

Conclusion

What effect do social isolation and environmental enrichment have on behaviour and brain plasticity? Was the question to answer in this essay. I believe that in this essay it became clear that social isolation has mainly negative effects on both behaviour and brain plasticity. Where this influence and the alterations in plasticity and brain functioning can result in a number of disorders. On the contrary environmental enrichment has mainly positive effects on behaviour and brain plasticity. The alterations seen in brain plasticity and functioning can be of help in the treatment and prevention of a number of disorders, such as the autism spectrum. This all indicates the importance of exposure to environmental enrichment and what risk the social isolation of billion of people during the COVID-19 pandemic can entail.

Afterword

I would like to use these last words of the thesis to thank my thesis mentor Robbert Havekes for giving the opportunity for and the help in writing this essay. I have learned a lot from writing this essay, not only about the subject of environmental enrichment, social isolation and its effect on behaviour and brain functioning. But also, about time management, scientific writing and literature research.

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