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Special issue on Alcohol Related Brain Damage: Classification, Prognosis and Management

'I would not put a thief in my mouth to steal my brains' *William Shakespeare, Othello*

Contents

Editorial

Special Issue: Alcohol Related Brain Damage (ARBD)

Articles

Conference Reports

AOB

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Mirror, Mirror on the Wall: The Role for Neuroscience in Comparative Psychotherapy Research

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Introduction

A recent report (18th June 2012) by Lord Layard of the London School of Economics states that "The under-treatment of people with crippling mental illnesses is the most glaring case of health inequality in our country" and recommends increased access to psychotherapy[1]. Evidence is accumulating that psychotherapy works, not only by changing behavioral processes, but also by modifying the anatomy of the brain in a variety of disorders, including depression, panic disorder, obsessive compulsive disorder and borderline personality disorder[2,3,4,5]. The question therefore is not whether psychotherapy is effective, but rather which type of psychotherapy should be used. There are dozens of different psychotherapy modalities available, ranging from a few sessions only to a few years of weekly sessions. Also, therapists' training varies from a few months to many years. It goes without saying that the costs vary tremendously too. Studies, which compare different types of psychotherapy with each other, abound, but do not provide a winner. Over fifty years ago, Rosenthal reported that the results are consistent and remarkable: a successful psychotherapy outcome is not predicted by the type of psychotherapy, but rather by the quality of the therapeutic relationship[6]. Twenty-five years ago, Senger explained this finding by the following parable: Imagine a shopper in a supermarket purchasing a rabbit stew and finding numerous brands for selection. The labels might include "Cottontail Stew", "Jack Rabbit Stew", "Belgian Hare Bourguignonne", "Generic Rabbit Hash" etc. Let us assume further that the fine print on each label states, "Contains Moose Meat as a filler". Let us assume further that truth in advertising does not require that the listing of ingredients be quantified. That is, even if the manufacturer adds an entire moose to a couple of rabbits, the mixture can still be labeled "Rabbit Stew". So it is with the psychotherapy market. There is an undetermined amount of powerful relationship factors (moose) in each brand of psychotherapy. The purchaser is not informed – nor does the provider know – how much of the nutritional value of the psychotherapy stew is due to "non-specific" moose or to "specific" rabbits.[7]

The concept that the degree of therapeutic alliance, but not the modality of psychological therapy, predicts a good outcome has since been borne out by time[8,5]. In fact, a critical review of the literature showed a lack of therapist empathy to be the best predictor of a poor outcome in psychotherapy (reported in[5].

This is a very striking finding, which muddies the waters of research into comparing different psychological therapy techniques. We find ourselves in a quandary,

comparable to the difficulties researchers faced in pharmacological trials before they realized that they had to control for the placebo effect. It is common knowledge now that in pharmacological research, the active ingredient of a medication can be tested only by comparing it to an inert but otherwise identical placebo. Randomized controlled double-blind studies, which are the gold standard of research, are designed to eliminate all forms of psychological confounders. Only by following this rigorous process can the true effect of a new medication be determined. Can we apply these principles to comparative psychotherapy research?

A whole issue of the Journal of Clinical Psychology in 2005 was devoted to exploring the interplay between the placebo effect and the therapeutic relationship[9]. One line of thought has been that psychotherapy is nothing but a placebo, where a placebo is defined as "a sham treatment that may be used clinically to placate a patient" [10]. Others have argued that the "common factors", e.g. therapist empathy and the strength of the therapeutic alliance, are essential ingredients to all psychotherapy success[11]. These common factors may show more variation between therapists than between different types of therapy. However, they are not a placebo, as they are "essential" and as such cannot be eliminated[12,13]. In other words, the common factors cannot be defined as a placebo, because they are not inert, but rather an integral part of the mechanism of action of psychotherapy.

According to Lambert problems with interpreting the results of comparative studies, as well as the common finding of no difference in outcome for patients who undergo dramatically different treatments, have led to calls for an end to the funding of these studies[13]. Nevertheless, a solution for this problem is essential to promote the evidence-based practice of psychotherapy[9]. As Wood suggests: "the research focus should now move from establishing the effectiveness of any one technique, towards studying what common mechanisms underlie all therapeutic contact" [14].

As yet, there is no objective way to measure or control for the quality of the therapeutic relationship[8]. Even though some studies include a questionnaire for both therapist and patient on the strength of the therapeutic bond, this is not sufficient[15,16]. Asking the patient what they feel about the therapeutic alliance is better than nothing, but does not have sufficient scientific rigor. In pharmacological studies it has been shown that it is not enough to ask a patient whether they think they have been given a placebo or not, one has to actually administer it in a double-blind controlled way.

Some may ask why we would want to know which type of therapy is the most effective if the data shows that it depends on the therapist-patient alliance, rather than the therapy? This is a fair point. However, if it were possible to get accurate data comparing the value of different types of psychotherapy, it would be invaluable for service planning, as the cost of different therapies varies widely. The government is currently promoting the cheapest option in the IAPT – initiative (Improving Access to Psychological Therapies), but is this really the best way forward? Also, a better understanding of how and why the therapeutic bond is so important may be useful in the training of therapists of all the different modalities to further improve success rates.

Back to basics: The evil stepmother

We now have a reasonable understanding of how a single brain works. What is less well understood, and more difficult to research, is what happens when two brains interact, as in psychotherapy. A recent publication examining the interaction between two individuals states that "social interaction is fundamentally different when we are in interaction with others rather than merely observing them", and refers to "social encounters" as the "dark matter", of which very little is yet known[17].

Several similarities exist between the therapist-patient and mother-infant interaction. Let us therefore first consider what is known of the communication between mother and infant brains, before turning to the neuroscience underlying the therapeutic relationship.

It is conceivable that the basis for all relationships is found in the mother's regulation of her infant[18]. Babies are born in a very immature state and are absolutely dependent on their caregiver for survival. Developmental psychologists have shown in elegant experiments how the good-enough mother modulates the infant's psychobiological state[19]. These experiences, which fine-tune the baby's neurodevelopment, are embedded in the communications between the mother's mature and baby's immature right brain hemispheres[19]. Shore, in his recent book "The Science of the Art of Psychotherapy", has convincingly shown that visual, auditory and tactile stimuli are communicated between the right brains of both mother and child[20]. These include non-verbal components of communication, such as tone of voice, gestures,

postures and facial expression[21]. Interestingly, most mothers cradle their babies on the left side, facilitating the input to their right hemisphere through the input from the left side of the visual field, the left ear, and sensory input from the left side of the body[18,20].

Mother are external regulators of their infant's psychobiology[20]. This occurs through various different stages, which all occur and reoccur within milliseconds. First there is attunement, i.e. the mother needs to be open to receive information from the infant. Auditory and visual information is received through her senses. This activates her mirror neurons, which internally reproduce the infant's psychobiological state[22]. Once she has understood that how the infant is feeling, she can modulate this by interacting with her infant. For example, if the infant cries, the good-enough mother picks up this distress, reflects back that she is concerned and is willing and able to help, and the baby is consoled[23]. The role of the caregiver is to help down-regulate negative affect, but also to up-regulate positive affect like curiosity and play[19].

This process does not need to be error-free. In contrast, it is often the misattunements, which are recognized and repaired, that are most important for the internalization of self-regulating capabilities[21]. As the baby's brain matures, these external regulations of its affect can be internalized and the individual can progressively master the ability to self-regulate affect[19].

The ability to regulate one's own internal state while tolerating and mirroring the distressed state of another is an emotionally demanding task, as parents and therapists will know[21]. Mothers, who have suffered trauma themselves, may be overwhelmed by their infant's distress and thus be unable to down-regulate it, which can lead to an intergenerational transmission of trauma[23]. As Schore has shown, the ability to regulate affect is imbedded in the right hemispheric cortical-subcortical circuits[20]. If individuals suffer trauma in childhood, they suffer unregulated hyperarousal of terror in abuse, or the unregulated hypoarousal of neglect. These states tend to occur for prolonged periods of time, as the caregiver who abuses or neglects, typically does not provide interactive repair. If a child has too few experiences of being regulated, it cannot internalize self-regulating capabilities and therefore tends to have a limited ability to regulate affect in later life[20]. These individuals are easily overwhelmed and are more susceptible to all forms of psychopathology. These are the people who are likely to end up being referred for psychotherapy[21].

To summarize: in situations where the initial experience of care was mostly "good enough", the child manages to internalize self-regulating capabilities. However, if the initial care experience fell short of the minimum requirements, often through neglect or abuse, this can be apparent in the inability to regulate affect in later life, predisposing such individuals to psychological problems and a need for psychotherapy[20].

Parallels in psychotherapy: the enchanted forest

Just as the mother-infant relationship is fundamentally a psychobiological dyadic system of emotional communication and affect regulation, this same system underlies subsequent relationships, including the therapeutic alliance[21]. The aim of psychotherapy is to help an individual develop the ability to navigate their life without continued support from a therapist. It can be argued that the role of psychotherapy is similar to that of a parent, in the sense that it promotes self-regulating ability, by providing external regulation until self-regulation capabilities are sufficient. As in the mother-infant relationship, the processes of attunement, understanding and reflecting back in a more containing way forms the basis of all psychotherapy[20]. It is conceivable that there may be an overlap between the qualities, which typify the good-enough parent, and that of the effective therapist.

The success of psychotherapy may depend on it serving as a corrective relational experience. The attachment literature has many examples of the benefits of a corrective relational experience. For example, children who have even a single good attachment relationship may be protected from long-term damage of abuse or neglect. Also, adults can become "earned secure" through a good relationship experience, whether this is through a partner, friend or therapist[19].

Different psychotherapy modalities rest to a large degree on verbal left-brain to left-brain communication[24]. Between adults, this would rest on hearing and understanding language and being able to formulate and express answers. Psycho-education, cognitive therapies and interpretations are thus, at least in theory, primarily left-brain, verbal processes. However, what patients may need most is a corrective relational experience, which is provided by right-brain to right-brain non-verbal emotional communication[21]. I propose the "common factors" among different

therapeutic modalities to be the mainstay of psychotherapy, because they rely on right-brain to right-brain communication between therapist and patient. In the delightful book "Clinical Intuition in Psychotherapy", such processes as therapist empathy, warmth, clinical hunches, play and humor are all shown to be right-brain processes[25]. In the therapeutic relationship between a therapist and patient, this non-verbal understanding is the key to therapy and healing[21].

As in mother-infant research, it seems that when we see gestures and facial expressions, or hear the pitch, rhythm and prosody of speech, we have a way of copying these in our minds. Mirror neurons fire in response to observing an action in someone else[22]. For example, if I see someone who is standing up, gesticulating wildly, frowning and shouting, my mirror neurons replicate these actions in my brain. I then feel my heart speed increasing, my blood pressure rising and my face frowning and become aware that it is anger that I am feeling. As my limbs and face have not really moved, I get the feedback that this anger is not my own, but that of the person I have been observing. I thus understand what he feels by unconsciously replicating his actions in a select few neurons in my brain, just enough to give me a taste of what he is experiencing so that I can understand it[22]. This process can be so powerful that people with intractable phantom pain from an amputated limb can get relief by seeing someone else's limb being massaged[26].

Mirror neurons act by non-consciously mimicking facial expressions and postures of others, letting us feel what others are experiencing[5]. The neurobiology of empathy thus relies on mirror neurons[5]. Even though the research on mirror neurons is relatively new, the process of internally experiencing what other are feeling was described by Freud more than a century ago. Freud coined the term countertransference to describe the feelings, which the patient elicited[27]. Personal therapy has been considered an important part of a psychoanalyst's training in order to become aware of their own issues, so that they may become more accurate in their use of countertransference to understand what the patient was feeling. In other words, if it is your job to accurately perceive what another is feeling, it is essential to polish your metaphorical mirror first. A central tenet in psychodynamic psychotherapy is to reflect one one's own feelings with curiosity, to wonder if they could be a reflection of what the patient is feeling, and to not automatically react to them. This creates a space for new possibilities, in which the therapist may respond in a way that would be helpful, rather than a knee-jerk reaction to what is projected on them by the patient[5].

In other words, accurately perceiving what another is feeling is just the first step. If one just reflected it back unchanged, that would be mocking and probably increase the other person's distress. In order to be a helpful therapist, one needs to rework this communication and reflect it back in a more contained manner. In mother-infant research it has been shown that the good-enough mother attends to her infant's distress, but then modulates it back in a less threatening way, so that the infant feels understood and contained[20]. A mother may for example pick up an angrily crying baby, while frowning and smiling simultaneously and speaking with exaggerated prosody. This lets the infant feel that the mother "got it", but is not overwhelmed and can help. In the therapeutic relationship, clinicians similarly need to let the patients know that they understand their distress, but are not (as) upset themselves and are still in a position to think clearly and to be able to help.

But how does this process get communicated back to the patient? It works the same way. Patients have mirror neurons too. A patient looks at the therapist and listens to their tone of voice, and hopefully if they are not too distressed they will be able to listen to what is communicated verbally as well. If the process runs smoothly, the patient will realize that the therapist has understood them, but is not overwhelmed. This realization may have a calming influence.

Also, the process of putting feelings into words enables the left and right hemispheres to become integrated[21]. This enables people to create coherent life narratives, which are associated with a secure attachment and ability to self-regulate affect[21]. Likewise an effective therapist is well-grounded in theory and technique (left-hemisphere processes), but also able to sense, express and regulate both the patient's and their own affective states, which are right-hemispheric processes[21].

Although the process of therapist empathy is now better understood, there is still no way to objectively measure therapist skill at sensing the patient's non-verbal communications.

The role for Neuroscience: the prince on the white horse

In order to be able to do comparative studies between different types of psychological therapies, one would need to control for the quality of the therapeutic bond, which is determined mainly by therapist empathy and right-brain to right-brain non-verbal communication. Thus, in order to develop a way of controlling for right-brain communications, so that left-brain techniques can be compared, a biological measure would be helpful. Also, if a reliable biomarker could be found, it could potentially guide a course of treatment and predict treatment outcome, instead of having to rely on costly trial-and-error approaches[5]. Psychologists are unlikely to have the necessary expertise and this is where neuroscientists can potentially come to the rescue. However, unfortunately many neuroscientists are not interested in psychotherapy. Of course it may all be part of the greater mind-body divide in which neuroscience and psychology are not happily integrated. But if one could bridge the gap, there are many potential avenues that could be explored.

In the intersubjective space between two individuals, who interact with each other, it is important to consider all aspects of their communication. Ideally one would like to measure as many parameters as possible in these interactions, to find out what gives the greatest reliability. Ian McGilchrist has written a remarkable book, called "The Master and his Emissary", in which he convincingly argues that the right hemisphere is the mastermind, controlling affect, the autonomic nervous system and the hypothalamo-pituitary adrenal axis (28). The left hemisphere, with its powers of language and logical thought, may be overvalued in Western Societies, to the detriment of the right hemisphere, which is able to grasp the whole, regulate affect and see the bigger picture[28].

The right hemisphere controls both the sympathetic and parasympathetic parts of the nervous system[28]. As it is not possible yet to directly measure unconscious central nervous system activity in real-time during psychotherapy, mapping the peripheral physiological response may be sufficient to deduce these[5]. Adler says: "To the extent that we are emotionally responsive to someone, we are physiologically responsive to them"[18]. Several studies have shown physiological changes in patients during psychotherapy, including changes in muscle tension, respiration rate, finger temperature and skin conductance (reviewed in[5].

Let us first consider the **sympathetic nervous system**. One of the central neuroanatomical structures identified in neuroimaging structures of empathy is the anterior cingulate cortex, which overlaps significantly with the brain structures that control fluctuations in skin conductance[5]. It may thus be possible to measure skin conductance, which is a result of sympathetic nervous system activation, to track changes in the anterior cingulate cortex and thus empathy[5]. Measuring skin conductance as a measure of sympathetic nervous system activation in both therapist and patient has been shown to be helpful therapeutically in a few studies (reviewed in[18]), and has recently been done with good results in a case study, leading to increased understanding by the patient and deepened empathy by the therapist[5].

On the other hand, changes in heart rate variability between therapist and patient may accurately reflect **parasympathetic nervous system** activation[29]. The right hemisphere is in parasympathetic control of the heart via its connections with the right vagal nerve in adults[29]. It is thus conceivable that heart rate variability, which gives a good measure of parasympathetic control of the heart, may also serve as an indirect measure of right hemisphere activity. Heart rate variability analysis provides a non-invasive way to monitor and record not only baseline sympathetic/parasympathetic balance, but also the magnitude and direction of instantaneous shifts in the autonomic balance in response to cognitive and emotional processes. An increase in heart rate variability is thought to accompany an improvement in physical and/or psychological state and may thus also serve as a measure of therapeutic success after a course of therapy[30,31].

There are two kinds of relationships between the measures of therapist and patient which may be of interest: a concordant relationship occurs when the variables move in the same direction, whereas a discordant one occurs if they move in opposite directions[18]. Both may be necessary for therapy to be successful, as therapists sometimes need to challenge their patients by seeking clarification, offering interpretations or confronting beliefs[5]. This is similar to the mother-infant literature, in which misattunements and rupture-repair sequences are essential for the development of self-regulating capabilities[23].
If we now consider the **endocrinological** system, it is known that the circulating levels of the majority of hormones are directly or indirectly under neurological

control. Although instantaneous changes, such as emotional shifts during therapy cannot be assessed through changes in hormone levels, it may be possible to evaluate the effect of a course of psychotherapy. Oxytocin is an obvious choice. Also termed the "hormone of empathy", it is known to be high in women after delivery and while breastfeeding, facilitating mother-infant bonding[32]. Vasopressin possibly fulfills a similar role in men[18]. There is some evidence that administering oxytocin as a nasal spray may improve scores in empathy tests for individuals on the Autism Disorder Spectrum[33]. The hypothalamus, which produces oxytocin, is controlled by the right hemisphere[28]. It would be interesting to know whether therapist oxytocin levels correlate with therapeutic success rates. Other potential biochemical markers would be: endogenous opioids for placebo-mediated analgesia and central cholecystokinin, which is involved in the nocebo response[32].The Hypothalamo-Pituitary-Adrenal axis is affected in depression and can be modified by psychotherapy, thus cortisol may be modified as well[4]. The possibility of investigating cortisol and oxytocin in saliva may make this a more acceptable option to patients and therapists alike.

The **immune** system is increasingly recognized to act both as a regulatory and sensory system. Immune processes are known to affect emotions and behaviour, e.g. when ill with flu, we feel miserable and curtail our actions. Pro-inflammatory cytokines such as Interleukin-1, Interleukin-2, Interleukin-6 and Tumour necrosis factor-alpha have repeatedly been shown to alter the functioning of a variety of neurotransmitters[34, 35]. On the other hand, thoughts and emotions can also influence immune processes, e.g. depressive rumination is associated with an increase in pro-inflammatory cytokines, which can adversely affect health[36, 37, 38]. It is known that proinflammatory cytokines are under tonic inhibitory control via the vagus nerve, with important implications for inflammatory diseases, including depression[39]. Psychological intervention in cancer patients has reduced both the levels of inflammatory markers and of depression scores[40]. It would be interesting to measure immune parameters before and after a course of psychotherapy, to see if therapeutic success could be linked to immune changes as well.

However, a proper understanding of physiologic responses to social interactions cannot be achieved by examining only one member of the sociophysiologic feedback loop[18] and thus the biological responses of both patient and therapist may need to be measured. There may be a resistance on the part of therapists to be monitored. Perhaps some therapists themselves are unaware that they are not really "neutral" and as such form an integral part of the relationship through which the patient changes.

It is possible that the mere act of measurement can change the therapeutic interaction. However, new totally non-invasive recording equipment and measures in saliva are available that all but eliminate this effect.

Conclusion: the happy ending

My hope is that this paper will stimulate a fruitful cooperation between Neuroscience and Psychotherapy. A marriage between these two disciplines will enable greater integration, to the benefit of both. Neuroscientists may learn more about the interaction between two brains in real time. Psychotherapists may learn how to measure and possibly improve the quality of their mirror neuron activity and right-brain processes. If a reliable biomarker were found, the strength of the therapeutic relationship could be controlled for in comparative psychotherapy research. This may provide the answer to the age-old question: Mirror, mirror on the wall, who is the fairest psychotherapy princess of them all?

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