Many cancer patients find the stresses and side-effects associated with chemotherapy physically debilitating – but their cognitive abilities often appear to be impaired, too. In the multicenter study COGITO, a team of researchers led by the psychologist Dr. Kerstin Hermelink of the Clinic of Gynecology and Maternity Care at LMU Munich has taken a closer look at the phenomenon of the “chemobrain”, and come to some surprising conclusions.

In 1970, Thomas Luparello and his colleagues at the State University of New York in Brooklyn carried out what has since become a classical experiment: Asthma patients were either given a drug known to dilate the bronchi of the lung and relieve asthmatic symptoms, or a bronchoconstricitor that would be expected to worsen their condition. Only some of the participants were correctly informed which agent they were being given. The rest were told that they were receiving one drug, but were actually given the other. When the researchers measured the physiological responses to the drugs, they found that lung function actually improved significantly in the group who mistakenly believed they had taken the remedial agent. Conversely, in those who erroneously thought they had been treated with the exacerbating drug, lung function was compromised. The results of this trial dramatically demonstrate the extent to which the effects of a drug may depend on what the patient expects it to do.

Things are rather more complicated in the case of patients who embark on a course of chemotherapy after having received a diagnosis of cancer. The agents used to kill malignant tumor cells are highly toxic, and often damage healthy cells as well. Side-effects such as nausea, vomiting, hair loss and fatigue are the result. Many patients, however, also have the impression that their cognitive abilities are adversely affected by such treatments. They report that they have difficulties concentrating, have become more forgetful, often fail to grasp simple problems and find routine tasks more challenging than before – and they attribute these changes to the chemotherapy they are undergoing. Indeed,
this condition has acquired a name of its own – “chemobrain” or “chemofog”. Scientific studies of the phenomenon have come to conflicting conclusions. Consequently, it remains unclear whether cognitive performance is indeed compromised by chemotherapy and, if it is, whether the effect is attributable to the pharmacological agents used or to some other factor.

COGNITIVE EFFECTS OF CHEMOTHERAPY IN DOUBT

A team of investigators led by Dr. Kerstin Hermelink of the Clinic of Gynecology and Maternity Care at LMU Munich and the neuropsychologist Professor Karin Münzel of the Department of Psychology at LMU, has been seeking answers to these questions since 2003. Their study, aptly dubbed COGITO (for “Cognitive Impairment in Therapy of Breast Cancer”), involved more than 100 breast cancer patients recruited from five treatment centers in Germany. Various domains of cognitive function, including attention, memory, mental flexibility and executive function, were tested prior to the start and shortly before the end of chemotherapy, and the tests were repeated 12 months after the baseline assessment. COGITO is one of the largest studies ever to probe mental abilities before, during and after cancer treatment. “The first studies on chemobrain were performed in the 1990s and appeared to confirm a link between cognitive deficits and chemotherapy”, says Kerstin Hermelink. “Up to 75% of the patients involved were reported to show cognitive compromise following chemotherapy.” In most cases, the effects detected were relatively mild and gradually disappeared after termination of treatment, but they affected a wide spectrum of functions. “However, many of these studies suffered from methodological weaknesses, so the significance of the results was difficult to assess”, says Kerstin Hermelink. “These studies lacked a baseline assessment: Mental abilities were measured during or after, but not before chemotherapy; and in most studies, the sample size was relatively small.”

Nevertheless, by the beginning of the 21st century, the notion that chemotherapy has a deleterious effect on cognitive function was widely accepted. “More rigorous studies performed since then, which avoided the design flaws that had marred earlier investigations, began to cast doubt on the idea”, reports Hermelink. “For example, two independent large-scale longitudinal studies were unable to find any evidence for a decline in cognitive ability in association with standard chemotherapy.”

The patients chosen for the COGITO study were between the ages of 18 and 65, had been diagnosed with invasive breast cancer with no evidence of metastases, and were randomised to receive one of two preoperative chemotherapy regimens according to a clinical trial protocol, followed by endocrine treatment when appropriate. “We measured cognitive performance with a battery of twelve neuropsychological tests that covered a wide spectrum of cognitive domains”, says Kerstin Hermelink. In addition, the researchers assessed current levels of anxiety and depression, the disposition to experience negative and positive emotions, and the patients’ self-perceived cognitive function.
Hermelink and her colleagues made several surprising discoveries. “It emerged that, in about one-third of cases, cognitive performance was worse than to be expected already before the start of chemotherapy”, reports Hermelink. Furthermore, after termination of chemotherapy, deterioration in cognitive abilities was detected in 27% of patients, but a commensurate subgroup, namely 28%, actually showed an improvement in their test scores, while the remainder showed no change. Practice effects were accounted for. “We conclude from these results that there must be other factors than the chemotherapy that affect cognitive function in cancer patients already before the start of treatment”, emphasizes Kerstin Hermelink. “During chemotherapy, these factors continued to have a damaging effect on a subset of patients while cognitive function was already recovering in others.”

In addition to monitoring effects of chemotherapy, the investigators also asked whether endocrine treatment with anti-hormonal agents like tamoxifen, aromatase inhibitors or GnRH (gonadotropin-releasing hormone) analogs affected mental abilities. These substances all lead to estrogen depletion or even induce premature menopause. “Estrogen acts on many tissues, including the brain”, explains Kerstin Hermelink, “but whether or not changes in estrogen levels have deleterious effects on cognition is controversial.” The COGITO study found no evidence for such an effect. Instead, premature menopause even had a positive effect on performance in some tests.

“Our results clearly show that the concept of the chemobrain is an oversimplification and – at most – explains the cognitive problems experienced by cancer patients during and after chemotherapy only in part”, says Hermelink. “We cannot rule out the possibility that chemotherapy does have a deleterious effect on brain function, but it is certainly not the sole trigger of cognitive compromise.” The researchers hypothesize that the major cause of deficits in concentration and memory might be the stress associated with the cancer
experience. It has long been known that persons who have experienced traumatic stress, for instance the victims of violence or survivors of natural disasters, may display reductions in cognitive performance. Traumatized patients also sometimes show changes in specific brain regions, in particular a reduction in the size of the hippocampus, an area of the brain which is known to be involved in the formation and retrieval of memories. These features are probably attributable to changes in the production and secretion of stress hormones. Most cancer patients too have to cope with increased levels of stress. Indeed, the diagnosis itself may impose such an emotional burden that its effect can be equated with a psychological trauma. The side-effects of chemotherapy may then add further to this emotional load. In future studies, Kerstin Hermelink and her colleagues therefore plan to ask whether stress might not be the real trigger for chemobrain. “Perhaps it would be more correct to refer to the condition as ‘stress brain’ or ‘crisis brain’”, she suggests.

The results of the COGITO study not only cast doubt on the underlying causes of cognitive deficits in the context of cancer therapy, they also raise questions about their very nature. “The cognitive problems that our patients complained of actually had very little to do with the deficits detected by our objective tests.” The neuropsychological tests indeed revealed cognitive deficits in some patients, but these were usually minor and, in most cases, were not noticed by those affected. Conversely, some patients complained of changes in mental abilities that could not be confirmed in the tests. “These results imply that neuropsychological tests do not measure the condition that patients complain about”, says Hermelink. “Previous studies have consistently reported similar observations, but their authors usually tried to explain the discrepancies away, for example by assuming that the tests used were not sufficiently sensitive and not close enough to the everyday experience of the patients”. Hermelink and her team have come up with a new model that might explain the perceived deficits that a subgroup of participants reported. The crucial observation was that many of the patients who complained of chemobrain also had elevated scores of negative affectivity and depression. They showed a marked disposition to harbor negative emotions such as anger, shame or feelings of guilt. “The subjectively perceived problems may therefore be connected with the patient’s underlying emotional state”, Kerstin Hermelink points out. “Such patients probably make the usual kinds of everyday mistakes that we all make from time to time. They mislay their keys or forget to make a promised telephone call. But they attach greater weight to such errors and interpret them more pessimistically than one normally would.”

One other factor was found to be correlated with a feeling of not being as mentally fit as before – the prospect of having to undergo a particularly aggressive form of chemotherapy. The patients who followed the more intensive course of chemotherapy reported greater losses in cognitive performance than those in the control group who received the milder form of treatment. The psychological tests, however, found no differences between the two groups. So here too, the patients’ expectations played a decisive role in how they experienced
the effects of therapy, just as in the case of the 1970 study on asthma patients. Dr. Hermelink is careful to emphasize that, although most complaints of a loss of cognitive abilities after chemotherapy could not be confirmed by objective testing in the COGITO study, all should be taken seriously. Sometimes, objective tests and subjective perceptions indeed point in the same direction. “One must always consider the individual case and then choose the appropriate treatment option.” In many instances, psychotherapy may help depressed patients. On the other hand, there is evidence that deficits that are wholly subjective in character can still be reduced by cognitive training. This is apparently yet another case where faith can move mountains.

Dr. Kerstin Hermelink has worked as a researcher and psychological counselor in the field of psychooncology at the Clinic of Gynecology and Maternity Care at LMU Munich since 2001. She was the initiator and principal investigator for the COGITO study, one of the largest longitudinal studies of “chemobrain” ever attempted.