Caffeine: a cup of care? An exploration of the relation between caffeine consumption and behavioral symptoms in persons with dementia

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GENERAL DISCUSSION

The work presented in this thesis aims to expand knowledge on the relationship between caffeine consumption and behavior in persons with dementia. As stated in the general introduction, we hypothesized that caffeine consumption and behavior likely interact in persons with dementia and that both an increase and a decrease in behavioral symptoms would be possible. The known stimulatory effects of caffeine suggest the possibility of an increase in behavioral symptoms by suppressing fatigue and inducing restlessness in persons with dementia. However, caffeine consumption might also reduce behavioral symptoms in persons with dementia by improving concentration, lessening overstimulation or due to the social aspect of caffeine consumption.

The studies in this thesis support the hypothesis outlined above, as both positive and negative relationships were found in the course of our studies:

- In our observational pilot study (chapter 1), a negative correlation was found between caffeine consumption and apathy and aberrant motor behavior (AMB), whereas a positive correlation was found between late evening consumption of caffeine and getting up in older persons with moderate to severe dementia resident in a dementia special care unit.(1)
- In two single subject trials (chapter 2), reduction of caffeine consumption decreased several behavioral symptoms, including agitation/ aggression, irritability, AMB and general restlessness, in one 85-year-old woman with Alzheimer's disease but did not influence the aggressive behavior of another person diagnosed with mixed type dementia.(2)
- In a thorough systematic review of literature (chapter 3) we found indications that caffeine can both induce and reduce behavioral symptoms in persons with dementia. However, no consistent effect of caffeine consumption on behavioral symptoms could be demonstrated.(3)
- In our large cross-sectional study (chapter 5), behavioral symptoms (e.g. agitation, disinhibition and depression) were most common in persons with a low caffeine consumption.

To answer the question 'can coffee use influence the behavior of persons with dementia', we will first take a closer look at the most recent pathophysiological insights concerning the main target receptors of caffeine in the brain and what is currently known about the role these receptors play in the changing brain of a person with dementia. Insights into caffeine, adenosine receptors (AR) and dementia changed during the course of our research and our findings contribute to these changes. We will then explore the possible influences of caffeine consumption and behavioral symptoms in persons with dementia. To fully appreciate our results, several methodological considerations will also be discussed, after which we round up with the clinical implications of our findings and suggestions for further research.

CAFFEINE AND ADENOSINE RECEPTORS IN THE BRAIN

Caffeine has several targets in the brain, of which the most commonly discussed is the nonselective antagonism of adenosine receptors. Caffeine also known to interfere with dopamine, serotonin,

norepinephrine, epinephrine, acetylcholine and glutamate neurotransmission in the brain,(4, 5) to induce direct release of intracellular calcium, to inhibit cyclic nucleotide phosphodiesterase and to block GABA receptors.(4, 6) However, the doses required to achieve the latter effects (on calcium, cyclic nucleotide phosphodiesterase and GABA) are beyond toxic levels in humans.(6) Caffeine also has a weak affinity for benzodiazepine receptor binding sites and can counteract or alter the effect of benzodiazepines on human behavior,(7) although it has been suggested that the level of caffeine needed to antagonize the benzodiazepine receptors is likely toxic in humans and the modifying effect of caffeine on benzodiazepines might therefore actually be mediated via the adenosine receptors.(7) Taken together, these data suggest that antagonism of adenosine receptors in the brain is likely to be the primary mechanism of action of caffeine.(6)

Adenosine has several regulatory functions, but the most important are thought to be maintenance of energy homeostasis in the body and neuromodulation in the brain.(8, 9) Within the brain, adenosine is known to affect the release of neurotransmitters, neuronal excitability, synaptic plasticity and neuroinflammation.(9, 10) Four distinct adenosine receptors have been identified to date, adenosine (A)1, A2a, A2b and A3, each of which shows different expression patterns in brain regions and synaptic sites and each has different effects.(8, 9) The A1 and A3 receptors both have inhibitory effects, while both forms of the A2 receptor are stimulatory.(9) Only the A1, A2a and A3 receptors are present in the brain. The A1 receptors are mostly present in the cortex, hippocampus and cerebellum,(9) and presynaptically-distributed A1 receptors inhibit the release of glutamate, dopamine, serotonin and acetylcholine,(8) whereas postsynaptically-distributed A1 receptors inhibit neuronal signaling and reduce excitability.(8) The A2a receptors are mainly concentrated in the striatum and are only weakly present in the cortex and hippocampus.(9) The A3 receptors have a moderate presence in the hippocampus and cerebellum and are less prominent elsewhere in the brain.(9)

The exact function of the ARs is still unknown, but the various roles of the AR subtypes are currently being unraveled using so-called knockout mice (KO; living mice in which a part of the DNA is artificially switched off).(9) (See table 1). However, in humans the ARs appear to have both overlapping and unique roles. A recent review of the role of ARs in mood and anxiety disorders(8) concluded that agonism of the A2a receptors increases depression-like symptoms, while agonism of the A1 receptors has antidepressant effects. In anxiety, agonism of A1 receptors had anxiolytic (reducing) effects, whereas antagonism of A1 receptors or non-specific antagonism of ARs induces anxiety-related behaviors.(8) The distribution of ARs in the brain, differences in synaptic sites and multiple subtypes of ARs together provide many different pathways through which brain functions can be influenced by AR antagonism. This complexity makes characterization of the specific functions of ARs more difficult.(9)

As discussed above, caffeine is a known non-selective AR antagonist that impacts several AR subtypes, showing effects that differ depending on acute or chronic use(11) and low or high doses.(12) The effects of caffeine are primarily meditated through the A1 and A2a receptors, and major differences and even conflicting effects on ARs are seen following either acute or

Table 1. Changes in behavior shown in AR knock-out (KO) mice(9)

Behavior	A1 KO mice	A2a KO mice	A3 KO mice
Mood		Reverse behavioral despair/antidepressive	More behavioral despair
Anxiety	More anxiety-like behavior	(Inconsistent)	Some anxiety, but attributed to hyperactivity
Aggression	Increased aggression	Increased aggression	
Psychomotor activity	(Nihil)	Reduced and increased psychomotor activity	

chronic intake of caffeine.(11) Chronic consumption of caffeine has various neuroprotective effects which are characterized by upregulation of the A1 receptors but stable expression of the A2a receptors,(11) resulting in a shift in the balance of ARs.(11) Our study participants(1, 2, 13) were probably chronic coffee consumers, but the influence on behavior of the expected shift in AR balance is still too poorly understood to allow clear prediction of expected outcomes. However, we know that the number of ARs in the brain normalizes between one and five days after cessation of caffeine consumption.(6) This rapid normalization suggests that the participants in the single subject trials(2) probably had a normalized AR balance within a week of the shift to decaffeinated coffee. Their behavior over the following two weeks during which alternately decaffeinated or caffeinated coffee was consumed might represent behavior uncolored by the effects of chronic caffeine intake. These single subject trials could therefore, inadvertently, provide additional insight into the potential roles of ARs in behavior. In one subject, no relation between caffeine consumption and behavior could be detected. However, in the other subject an increase in behavioral symptoms consisting mainly of aggression and aberrant motor behavior was seen as caffeine was reintroduced during the second week. Interestingly, the item scores for these behavioral symptoms following the decaffeinated washout period were lower compared to the baseline (caffeinated) score prior to washout, suggesting that antagonism of the A1 receptor might be the main driver of behavior in this person with dementia. However, as this observation was confined to a single individual, firm conclusions cannot be drawn regarding the impact of the ARs on behavior and further research will be necessary to explore these intriguing preliminary insights.

In addition to the differences that occur following acute or chronic use, caffeine may also have biphasic effects, with differences in effect apparent between low and high doses.(12) In chapter 5, this biphasic effect was observed for the NPI item disinhibition and depressive symptoms as measured with the MDS-DRS. The exact mechanism underlying this biphasic effect is as yet unknown, but several mechanisms have been proposed(12):

1. Differences may be due to individual variation, some of which appear to have a genetic origin.(12)
2. The effects of low dose caffeine are mediated through mechanisms that are distinct from those of high dose caffeine. The inhibition of phosphodiesterase (PDE) has been suggested as a possible mechanism controlling some of the effects of caffeine.(12)

3. The biphasic effect might be due to the involvement of A3 receptors. In both A1 receptor knockout mice, A2a receptor knockout mice and control mice high dose caffeine influences behavior in a similar manner. However, A3 receptor knock-out mice showed a different response to caffeine than control mice at a dose that failed to produce a difference in A1 and A2a knock-out mice. The authors conclude that the A3 receptors may be responsible for the effects of caffeine following high dosages.(9)

Although antagonism of ARs in the brain is thought to be the primary mechanism of action of caffeine, nevertheless the involvement of different subtypes of ARs, the effect of AR upregulation with chronic caffeine use, the influence of the ARs at different brain sites and the dose response effects of caffeine all remain unresolved. A clear description of the mechanisms through which caffeine influences behavior, even in healthy persons, is therefore still lacking.

ADENOSINE RECEPTORS AND THE CHANGING BRAIN IN PERSONS WITH DEMENTIA

Dementia is a neurodegenerative disorder and the expression of the adenosine receptors is known to change with disease progression. In persons with Alzheimer dementia, the A2a receptors are increased in the hippocampus and cerebral cortex,(10, 14) A1 receptor density is reduced by 40-60% in the hippocampus and striatum, (10, 14) and both A1 and A2a receptor levels in the frontal cortex are increased in either the early or advanced stages of Alzheimer's.(15) It has been suggested that A1 receptors may play a role in the pathogenesis of Alzheimer dementia, and that modulating the A2a receptors might have neuroprotective effects during progression.(14) While the impact of changes in the expression of ARs on behavior during the progression of dementia is presently unknown, the fact of changes suggests that the influence of caffeine is also likely to change.

CAFFEINE AND BEHAVIOR IN PERSONS WITH DEMENTIA

Taking into account the results of the studies presented in this thesis, the known functions of ARs and the changes that occur during the progression of dementia, the relationship between caffeine consumption and behavior in persons with dementia is either immensely complex or very straightforward. Previous studies have reported associations between behavioral symptoms and caffeine consumption in persons with dementia, but the direction and size of effects varied to such an extent that if we were to pool results, the net effect would be close to zero. The straightforward explanation is that all study results are coincidental or biased, and there is no consistent association between caffeine use and behavior.

A more complex and nuanced explanation is that the relationship between caffeine and behavioral symptoms is multifactorial, and factors influencing associations most likely include personal differences, dosage, chronic use, progression of neurodegenerative diseases and other multimorbidities. We discuss these factors in more detail below.

The effects of caffeine differ, even among healthy adults, and these differences are known to affected by many factors, for example the polymorphisms in cytochrome P450 CYP1A2, which metabolizes caffeine, and adenosine A2a receptor, which is the target of caffeine in the brain and is thought to be responsible for most of the behavioral effects.(16) There is also no evidence to suggest that individual sensitivities to caffeine disappear in the event of dementia. Consequently, and similarly to healthy adults, some individuals with dementia will be unaffected by caffeine while others will have sleeping difficulties after just a single cup of coffee in the afternoon. This pattern was also seen in the single subject trials.(2) Healthy adults tend to adjust their personal caffeine consumption to minimize the adverse effects or maximize the benefits, but persons with dementia are unlikely to be able to self-adjust caffeine consumption and may therefore be more prone to suffer adverse effects.

As discussed, the effect of caffeine on behavior is generally attributed to antagonism of adenosine receptors, but when consumed in high doses caffeine may no longer act as an adenosine antagonist(12), whereas low doses might not reach the threshold for effect. Depending on specific circumstances, the dose-dependent effects of caffeine might follow both a straight line and a U (or inverted U)-shaped curve, as described in chapter 5.

Different effects on behavior are seen upon chronic versus acute consumption of caffeine,(17-19) an outcome most likely due to upregulation of the A1 receptors shifting the balance of ARs.(11) In addition to the upregulation or ARs due to chronic consumption, dementia is a neurodegenerative disease that also may influence adenosine receptors in the brain, leading to effects of caffeine that may differ amongst healthy persons, persons with mild dementia and persons with severe dementia.(3)

To summarize, current evidence suggests that the individual, the disease (dementia), the intervention (caffeine) and behavior may all be interdependent, resulting in a very complex relationship between caffeine and behavioral symptoms in persons with dementia.

KITWOOD'S EQUATION

The complexity of the relationship between caffeine and behavioral symptoms in dementia can also be explored using Kitwood's equation. Kitwood stated that the symptoms of dementia can be understood as an interaction between neurological impairment (NI), physical health (H), psychological factors (P), personal biography (B) and the social context [social psychology] (SP):(20)

$$D = NI + H + B + P + SP$$

NI ↓ = A recent systematic review concluded that consumption of coffee, tea and caffeine or higher plasma caffeine levels may protect against the onset of dementia, but the evidence was too limited to draw conclusions regarding an effect on the progression of dementia. (21) Although an exact mechanism has yet to be identified, it has been suggested that caffeine might directly reduce amyloid beta production in the brain(22) and thus have a direct influence on neurological impairment in persons with dementia.

H ↕ = Caffeine has widespread pathophysiological effects on the body, both positive and negative. On the positive side, due to adenosine antagonism and a vasoconstricting effect, caffeine is known to reduce pain, especially when taken in addition with regular analgesics. (23) In our cross-sectional study (chapter 5), pain was tested as a possible confounder and was found to influence the association between caffeine and the NPI-item lability. Caffeine is also known to induce cardiac arrythmias, especially in persons with preexisting cardiac comorbidity. The physical health of a person with dementia can be influenced by caffeine but depending on the comorbidity, caffeine might improve or worsen physical health.

P ↕ = Mood and anxiety are among the psychological factors that can impact the behavior of a person with dementia. In some adults, consumption of high doses of caffeine can lead to increased anxiety,(18) but a similar relationship has not been found in studies of persons with dementia(3) (as presented in chapter 3 of this thesis). In our latest study (presented in chapter 5 of this thesis) the group with high caffeine consumption had less anxiety compared to the group with low caffeine consumption, when corrected for the clustered design. In humans, both high and low caffeine consumption seems to be associated with anxiety. Caffeine is a non-selective adenosine antagonist, and the adenosinergic system has a role in both the etiology and treatment of depression and anxiety.(8) Studies in rodents have helped unravel specific roles of the adenosine receptors in anxiety, as knockout of the A1 and A2a adenosine receptors increases anxiety-like behavior in mice(8), while overexpression of the A2a receptor in mice resulted in a decrease in exploratory behavior (also indicative of an increase in one aspect of anxiety).(24) Just as A2a knockout and A2a overexpression both result in behavioral changes indicative of increase anxiety in mice, human consumption of caffeine results in a similar pattern of anxiety-related changes.

In chapter 5, we also found that depressive symptoms were lower in the group with normal caffeine consumption compared to the group with low caffeine consumption, an outcome consistent

with findings in healthy adults.(18) (25) Although the exact mechanisms are not (yet) known, it is clear that caffeine can have a direct influence on depressive symptoms and anxiety in persons with dementia.

SP ↑ =

The effects of caffeine are not limited to the physical and psychological, the consumption of caffeine-containing beverages also has a strong social aspect, as the social consumption of coffee is the customary way to ingest caffeine. Having a cup of coffee together with others, sitting quietly, chatting or reading a paper are all regular social rituals. According to the Unmet Needs Model by Cohen-Mansfield, unmet needs for social contacts or social activities can lead to behavioral symptoms in persons with dementia.(26) Both the Dutch(27) and the UK Alzheimer foundations(28) advise caregivers to take social activities into account when faced with behavioral symptoms. Although having a cup of coffee together is not specifically mentioned, it can act as a calming social ritual as suggested in one study.(29)

$D = NI + \mathbf{H} + B + \mathbf{P} + \mathbf{SP}$

Example 1. Less neurological impairment and pain, improved mood and a strong social effect of caffeine consumption leading to less behavioral symptoms.

$\mathbf{D} = NI + H + B + P + SP$

Example 2. Sleeping difficulties due to caffeine consumption, resulting in agitated behavior during the day.

$D = NI + H + B + P + SP$

Example 3. No changes in health or other factors in the equation due to genetic factors.

Accordingly, and depending on genetic variation, age, gender, sensitivity to caffeine, severity of dementia and any comorbidity, the equation of dementia might be influenced in specific ways by the consumption of caffeine (see examples).

METHODOLOGICAL CONSIDERATIONS

Although the studies presented in this thesis are very different in design, size and level of evidence, they all share certain strengths.

Firstly, these studies were the first of their kind to study the effects of caffeine on behavior in persons with dementia. During the progression of the studies that make up this thesis, a stepwise design was used that started with a small pilot study and a single subject trial to test whether the hypothesis was sufficiently robust to justify the later, larger studies. The combination of both small and large studies provided important insights into the complexity and treatment possibilities of caffeine in the behavioral symptoms of dementia.

Secondly, these pragmatic studies were all conducted with frail older persons representing the reality of the nursing home resident, in contrast to most medical research that unfortunately excludes older persons with dementia or persons with multimorbidity, resulting in limited evidence concerning this rapidly expanding group. In the pragmatic observational (chapter 1) and cross-sectional multicenter (chapters 4 and 5) studies the caffeine consumption was not altered or regulated. The results of these studies are based on normal caffeine consumption, instead of

the extremely high caffeine dosages regularly seen in caffeine research.(18, 30) Thus the influence of withdrawal is expected to be next to nothing. The conclusions from these studies can therefore be reliable extrapolated and offer directly applicable insights on caffeine consumption and behavioral symptoms in patients with dementia.

Thirdly, a common bias in food research is the recall bias. An example is smoking or alcohol consumption: participants (unconsciously) want to put themselves in a better light by underestimating the number of cigarettes or liters of beer they consume. But the other way around is also prevalent, for example the overestimation of the amount of vegetables one consumes in a day. The recall bias is also seen in caffeine research.(31) However, in the three studies to chance of a recall bias is small as the amount of caffeine consumed was observed and noted during the same shift, not recalled later.

Lastly, most studies research high-tech, theoretical interventions aimed at tomorrows' patients. Our studies of caffeine are unique in the sense that this is an intervention for todays' patients and current patients with dementia will benefit from the results.

However, to fully understand the results the following weaknesses have to be taken into account.

Firstly, persons with dementia were treated as a single study population, even though dementia is an umbrella term covering over 100 different diseases. Much is still poorly understood regarding the impact of disease on the brain in persons with dementia (a 'black box brain'). As caffeine influences brain neurotransmitters, it is possible that effects of caffeine differ depending on a specific disease or its stage. In a larger study, subgroup analysis based on major causes of dementia could be conducted to test whether this hypothesis is valid.

Secondly, a wide variety of behavioral symptoms were included in these initial pilot studies, including scores for several total scales. As caffeine may both induce and reduce behavioral symptoms, symptom-specific follow-up research would be advisable, preferably tailored to the individual.

Thirdly, in chapter 5 we described the dose-dependent effects of caffeine might follow both a straight line and a U (or inverted U)-shaped curve. Although our results do not stand alone and the response threshold and receptor regulation can be an explanation for the observed effects, severe design errors like a differential misclassification error can also lead to a reversal of results. However, in the studies in this thesis the measurements of the caffeine consumption and the scoring of behavioral symptoms was done by different persons and at the moment of scoring the participant was not yet assigned to a specific group. Therefore, the chance a structural severe differential misclassification influenced the results of both of these studies is small. However, there is a risk of non-differential misclassifications like incorrectly quantifying the amount of caffeine consumed (e.g. by over- or underestimating the amount of coffee in a cup or the amount of caffeine in the coffee). During the studies these measurements were standardized were possible and the amount of caffeine was calculated based on the way the coffee was brewed. When the brewed method was unknown or there was no average caffeine level know for the brew method,

the caffeine consumed could not be estimated. It is therefore possible the amount of caffeine is over- or underestimated, however, the best guess possible was made.

Fourthly, there are factors that are both associated with caffeine consumption and with behavioral symptoms in patients with dementia. In the multi-center cross-sectional study corrections were made for all know confounders. Due to the possible widespread influence of caffeine as shown in the paragraph 'Kitwood's equation' there is a potential of residual confounding. A lot of possible confounders were included in the study (see chapter 4 for the complete list of measurements). Several psychosocial and other lifestyle factors were not included in the study. All of the participants lived in nursing homes and had, at least at the moment of study, a similar general lifestyle. However, it is possible different nursing homes have different styles and thereby influencing both caffeine consumption and behavior. Although we did not correct for lifestyle as a single confounder, a correction for the nursing home (the clustered design) was made. However, residual confounding cannot be ruled out completely.

Finally, parts of this study were embedded in the Elderly Care Training Program. This program made it possible to collect data on cognition, caffeine consumption and behavior in a larger number of elderly nursing home residents (as described in chapter 4(13) and 5), but also required us to limit inclusion to persons with diabetes and thereby limit the range of possible inclusion. As far as we now there is no relation between diabetes and caffeine consumption or diabetes and behavior in elderly patients, so the selection of participants was unrelated to their behavior and their caffeine consumption. The results of the study are most likely also valid for patients with dementia without diabetes. However, this design has one important potential weakness: is the risk that trainees are more prone to make mistakes in data collection than trained researchers. However, as the trainees were supervised by senior researchers and subsample cross-checking was conducted to identify potential mistakes, we believe that any risk was minimal. Therefore, we stand by the results of this study and consider them reliable.

Despite these possible limitations, the studies described in this thesis provide unique insights into the relationship between caffeine and behavioral symptoms in persons with dementia, and have clinical implications that could benefit today's patients (discussed below).

CLINICAL IMPLICATIONS

As mentioned above, if one assumes that any association will necessarily be unidirectional and consistently linear, one might draw the conclusion that there is no relation between caffeine and behavioral symptoms in persons with dementia and, therefore, no clinical implications. However, this thesis provides data to support the argument that there is a relationship between caffeine and behavioral symptoms in persons with dementia, and this relationship differs per person, is dose-dependent, and changes with age and the presence of dementia.

However, even if we accept the relationship between caffeine and behavioral symptoms in persons with dementia as proven, there will still be some individuals in whom the consumption of caffeine has no effect on behavioral symptoms. Conversely, some individuals with dementia will show a (strong) response following consumption of caffeine. As caffeine consumption is an easy-to-manage intervention against the background of hard-to-manage behavioral symptoms that place a major burden on caregivers and reduce the quality of life of the person with dementia, it is advisable to take caffeine consumption into account when planning a stepwise, individualized approach to behavioral symptoms. While caffeine isn't one of the 'usual suspects' in behavioral symptoms, there is enough evidence to argue that it should at least be included in the line-up.

A stepwise, personalized approach to behavioral symptoms in persons with dementia should include a detailed analysis of the individual and their surroundings. In the diagnostic approach, we look for probable or possible contributory factors in a multidisciplinary journey into known behavioral symptoms such as pain, psychosis, infections, or over-stimulation, while also considering the unknown, unmet needs of a person who is incapable of communicating needs in any other way. The evidence is clear: caffeine is not just another ingredient in a drink. It should be included in the vocabulary of the professional as a possible influencing factor, similarly to over- and under-stimulation, toothache, constipation and miscommunication. If an analysis shows new agitation that started directly after admittance to a dementia special care unit and no other probable explanations are identified, a detailed analysis of the differences between home and nursing home might show a switch from decaffeinated to caffeinated coffee, suggesting that a switch to decaffeinated coffee is worth a try. Analysis might also show a significant decrease in coffee consumption on admission, in which case an increase in coffee consumption is also worth a try. It might also show that at home the person with dementia always went for a small walk in the garden after a coffee break. In terms of caffeine, analysis of behavioral symptoms involves not just asking 'do you prefer your coffee black, or with milk or sugar?' but taking into account all the nuances of coffee, such as 'do you prefer filter or espresso, black, with milk or sugar, at what time would you like the coffee, with a newspaper or a conversation, etc.'

FURTHER RESEARCH

In medical research, the ultimate proof of an intervention is a randomized controlled trial that is designed to prevent factors other than the intervention from influencing outcome by standardizing participants, measurements and the intervention itself.(32) This evidence-based method has been called into question, as it's based on standardized situations which simplify reality and ignores the multifactorial nature of daily practice. To put the evidence into practice, nuances of the evidence are needed. Therefore, the Dutch Council for Public Health and Society recommends that evidence-based medicine should be extended to embrace the context of the person.(32) If we hold to standard evidence-based practice, confirmation of the relationship between caffeine

and behavior remains unlikely due to the complexity of this relationship. However, when the context of the person is taken into account, a complex relationship between caffeine and behavioral symptoms suddenly becomes probable. We would therefore argue that the results concerning the effect of caffeine on behavior in persons with dementia warrant further research.

In our opinion both experimental and fundamental research into this subject is needed. At the moment, changes occurring in the brain of persons with dementia are poorly understood, but more research in this area could lead to potential new interventions for future patients with behavioral symptoms and dementia, perhaps also including more detailed insights into the effects of caffeine on the brain or even clues for additional interventions. However, persons with dementia who have behavioral symptoms today will clearly not benefit from these studies. These people require interventions now. The research detailed in this thesis shows that caffeine could be one such intervention but a clearer picture is needed. As changes to the brain and the sensitivity to caffeine of persons with dementia are both individual, a traditional randomized controlled trial will not suffice to provide clarity. The ideal design should include the context of the person, and cover both individual and group effects. An approach including the context of the patient could involve either a large series of single subject trials or a randomized controlled trial with goal attainment scaling. As stated in chapter 3, the single-subject trial is a randomized blinded study with one single patient. Usually it has a crossover design in which an intervention and a placebo both are tried multiple times to determine which is more beneficial.(33) It is seen as the ultimate proof for the individual patient(34, 35), especially if the intervention has shown individual variation in efficacy (35) like caffeine. Although a single single subject trial is the ultimate proof for a single patient, several single subject trials can be combined to estimate a population effect(33) and identify distinguishing features between those who benefit and those who do not benefit from the intervention.(35) Another practical element in this approach is that the single subject trials might differ slightly in design as long as the design is robust and the results are valid.(35) This means the design can be matched to the specific circumstances of the patient with dementia, the caffeine consumption and the behavioral symptoms involved, e.g. a longer washout period in patients with hepatic impairment or an extra crossover period. In an randomized controlled trial with goal attainment scaling, the design is standardized but for each participant a personal outcome (goal) is defined.(36) However, every goal is scored in a standardized way: a 5-point Likert scale ranging from '-2: much less than expected' to '+2: much more than expected'). In both methods, the large series of single subject trials and the more traditional randomized controlled trial with goal attainment scaling, the outcomes are defined for a specific participant. In addition, in the single subject trials the design could also be slightly altered to fit a specific participant better. As both are some kind of randomized controlled trial, their ideal designs have several similarities but some remark differences. In the table the headlines of these two possible designs for further research are illustrated.

These study designs need to be worked out in more detail and several caffeine related challenges have to be specified. First, the way of measurement of caffeine has to be defined. To

Table 2. Overview of two different study designs for further research into the effect of caffeine consumption on specific behavioral symptoms in patients with dementia

Study type	Series of single subject trials	RCT with goal attainment scaling
Participants	Patients with dementia who consume caffeine, and have behavioral symptoms in which caffeine is expected to have a positive or negative influence	Patients with dementia who consume caffeine, and have behavioral symptoms which are thought to be negatively influenced by caffeine consumption
Estimated number of participants needed	60	120
Randomisation	ABBAAB	Participants are randomized in two groups: intervention and control
Study period	6 periods of a week each (length of periods adjustable to the participant)	Two-week baseline and two-week intervention period, followed by a two week return to normal
Intervention/ 'A'	Caffeinated coffee and tea, in standardized cups and brew method	Decaffeinated coffee and tea, in standardized cups and brew method
Control/ 'B'	Decaffeinated coffee and tea, in standardized cups and brew method	No adjustment in caffeine consumption
Outcome measurements	For each participant an individual target behavioral symptom is defined, including the scale or index used to score and the preferred outcome	Goals attainment scaling: a personal goal per participant and the standardized scoring system. In addition, the NPI-NH for every participant once during every study period.
Blinding	Caffeine consumption and behavioral symptoms scored by different professionals. Study period blinded for the participant and professionals.	Caffeine consumption and behavioral symptoms scored by different professionals. Study group blinded for the participant and professionals.

determine the relation between caffeine consumption and behavior in patients with dementia, a continuous measurement of caffeine levels in combination with a continuous observation of behavior would yield the most precise results. The continuous measurement of caffeine levels bypasses the individual caffeine metabolism, but it does not surpass the individual ARs layout in the brain. So, we would know how much caffeine was in de blood during behavioral symptoms, but not how the brain is affected by the caffeine, so the added effect is limited. A single measurement of plasma caffeine levels might be arrangeable in nursing homes, but the added value is even less due to the same reason. If the purpose of the study is to measure the clinical effect, then the observation of ingested caffeine is sufficient, cheap and practical. However, the second specification has to be the way the caffeine is ingested. Caffeine can be administered in different ways: by injections, capsules or cups of coffee (with or without added caffeine). If caffeine is given by injection or capsule, the dosage of caffeine is exact. The amount of caffeine in coffee differs between the coffee bean used, the way the coffee is made and several other factors. Depending on the study goal, the preferred way of administering the caffeine can differ. An intervention trial into the positive effects of caffeine would probably have more use for a standardized dosage

which can be easily administered like a capsule. A trial into the etiology of behavioral symptoms and the role of caffeine would benefit more by including to normal caffeine consumption, like cups of coffee. To make an estimated guess of the caffeine consumed, the cup size and the brew method have to be included in the design. The other effects of caffeine in the body also have to be taken into account: adding more caffeine can have physical effects confounding the results, which makes a continuation of normal caffeine use more appealing for research in the frail population.

If the methodological challenges into caffeine research, behavioral research and research in frail elderly patients with dementia are taken into account, there are several reliable and valid study designs possible for further research. However, to make the designs feasible in complex situations like elderly care a certain amount of pragmatism is needed for researchers.

CONCLUSION

This thesis suggests caffeine has a place in a detailed analysis of behavioral symptoms in persons with dementia. However, advice on the treatment of behavioral symptoms cannot be given for a group of persons with dementia. As always, this depends on the multidisciplinary analysis of contributing factors.

A simple question: a complex answer
Coffee can influence behavior in persons with dementia, but most likely not in all persons, not in all situations and not all of the time; but it can have an influence. Therefore, it is recommended to consider caffeine as a possible moderator in the clinical assessment of behavioral symptoms in persons with dementia.

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